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Brain Activation by Visual Food-Related Stimuli and Correlations with Metabolic and Hormonal Parameters: A fMRI Study

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Abstract: Regional brain activity in 15 healthy, normal weight males during processing of visual food stimuli in a satiated and a hungry state was examined and correlated with neuroendocrine factors known to be involved in hunger and satiated states. Two functional Magnetic Resonance Imaging (fMRI) sessions were performed with a one week interval, after overnight fasting or 1 hour after a standardized meal. Blood samples and appetite assessment were obtained after each fMRI session. Main effects of processing food versus non-food stimuli were observed in the ventral visual stream, including the fusiform gyrus and hippocampal areas bilaterally, significantly more in the fasting state. Leptin concentration correlated negatively with activity in the left hippocampal area and right insula during the satiation condition. A positive correlation between ghrelin and "thought of food" hunger scores were found. The positive correlation between ghrelin and food related activation in the insula areas and the right hippocampus during fasting did not reach significance.

Conclusion: The increased activation of food *vs* non-food pictures in the ventral visual stream reflects increased salience of food pictures when subjects are hungry. Leptin was associated with activations in areas involved in processing of new information and emotion.

Keywords: Amygdala, fMRI, ghrelin, hippocampus, leptin, visual stream.

INTRODUCTION

The neurophysiological processing of food-related stimuli is increasingly considered relevant for the understanding of appetite regulation and the pathogenesis of obesity. Single-cell recordings in primates have shown neural activity related to food stimuli in the amygdala and the orbitofrontal cortex (OFC) [1,2]. In the amygdala, information regarding biologically relevant stimuli such as food is generally perceived, and forwarded to other brain regions such as the ventromedial cortex for further processing of its rewarding value or motivational salience [3-5]. Functional neuroimaging modalities such as functional Magnetic Resonance Imaging (fMRI) have been used to locate specific brain areas related to the perception and processing of food related stimuli in humans. Regional brain activity associated with perception of food stimuli is likely to depend on the state of hunger and satiety, presumably reflecting processing of motivational significance of food stimuli in addition to sensory effects [4-6 for an overview]. An interaction between perceptional, motivational and cognitive factors and changes in regional cerebral blood flow in the amygdala and orbitofrontal cortex using positron emission tomography (PET) has been demonstrated, supporting the theory that these areas constitute an integrated neural system critically involved in making adaptive responses and guiding decision making [5,7,8]. In a ^{15}O-PET study, it was shown that other limbic structures such as the nucleus accumbens and the insula seem to participate similarly in mediating physiological and motivational states [9]. LaBar *et al.,* used fMRI to assess the influence of hunger on the response of the amygdala and its related cortical structures. Their results showed that food related visual stimuli were associated with a greater response in the amygdala, parahippocampal gyrus, and anterior fusiform gyrus when participants were hungry. These findings further support the hypothesis that these regions are involved not only in visual processing but also in the integration of subjective interoceptive states [10]. However, in both studies, subjects were scanned using a fixed-order design, which may have biased their results [8,9].

Several hormones, for example ghrelin, leptin and insulin, have been shown to be involved in the central regulation of appetite, hunger and satiation [11-13]. Receptors for these hormones have been found in the hypothalamus, and the involvement of these hormones in the energy homeostasis and food intake has widely been

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hypothesized [14-16]. These receptors are also expressed in other areas of the brain such as the hippocampus and pituitary. One of the most important adipokines, leptin, has been implicated in a variety of functions of the central nervous system such as learning and memory processes, neuroendocrine regulation, and possibly neuroprotection [17-20]. Leptin replacement in genetically leptin-deficient adults modulates the sensitivity to visual food stimuli, with reduced activation in hunger related areas and enhanced response in regions involved in satiation [21,22]. Likewise, metabolic factors such as glucose and free fatty acids (FFA) are likely to serve as regional modulators of postprandial neuronal events [23]. It is therefore relevant to include measurements of these factors when studying brain responses to food related stimuli under various conditions, but to date studies on this issue have been scarce.

Another relevant aspect of the reaction to food stimuli is the role of craving, which can be defined as an intense desire to eat specific food types and is likely to influence the development of obesity, although the process of craving is still insufficiently understood. The neural correlates of food craving have been investigated with fMRI, showing activation in areas such as the hippocampus, insula and caudate nucleus, which have also been implicated in drug craving [24]. In another study, viewing chocolate pictures was associated with increased activation of the ventral striatum in cravers compared to non-cravers, highlighting the importance of these regions in making salience judgments regarding food stimuli [25].

The present study was designed to further investigate processing of visual food stimuli both in a satiated (one hour after food ingestion with a standardized meal) and hungry (after 12 hour fasting) state, in randomised order on two separate occasions to avoid order effects [8,9]. A second aim was to evaluate correlations between hormonal measurements and regional brain activity. To this end, we employed fMRI during presentation of food and non-food pictures in a crossover design, during which memory encoding and retrieval performance was registered, since it has been shown that memory for food items is associated with amygdala activity [9]. Also to evaluate some important modulatory factors, ghrelin, leptin, insulin, glucose and free fatty acids were measured both during fasting and satiated conditions. We hypothesized that responses to food *vs* non-food pictures would be greater during the fasting state relative to the satiated state, in areas known to be involved in processing visual food stimuli. Furthermore, a positive correlation between activity in these areas and ghrelin was expected, as ghrelin is an orexigenic hormone and its receptors have been located in the hippocampus and ventromedial hypothalamus. In contrast, during the satiated state we expected to find correlations between the satiation signals leptin and insulin and activity within the hypothalamus.

In conclusion, to further investigate the processing of visual food stimuli during a satiated and fasting condition, food and non-food pictures were presented during an fMRI procedure. Memory encoding, retrieval performance and several important modulatory factors were evaluated.

METHODS

Subjects

Fifteen male subjects were included. Data from one subject had to be discarded due to scanner failure, leaving 14 subjects for subsequent analyses. Inclusion criteria: male, age: 20-40 years, BMI 20-25, right handed, healthy. The subjects' health was determined by medical history, physical examination and laboratory screening tests. Exclusion criteria: left handed, a history of neurological or psychiatric disorder, use of medication.

Mean age was 23.4 ± 3.5 years, range 19-27 years, mean BMI was 22.4 ± 2.0 kg/m². Written informed consent was obtained, the study was approved by the Medical Ethical Committee of the VU University Medical Center and was conducted according to the principles of the Helsinki Declaration.

Design

With a one-week interval two fMRI sessions were performed at the same time in the morning, either after 12-hour overnight fasting or 1 hour after consuming a 1600 kcal standard meal in randomised order. The meal consisted of 44.4 energy % carbohydrates, 15.8 energy % protein and 39.8 energy % fat to provide a clear contrast between the fasting and satiated setting.

After each fMRI session, a 10-point Likert scale Appetite assessment score was obtained, consisting of items on hunger, fullness, desire to eat, prospective consumption, and total appetite [26]. Also, blood samples were collected for measurement of plasma glucose, free fatty acids, triglycerides, insulin, leptin, and ghrelin.

Scanning Procedure

A 1.5 Tesla Sonata MR scanner (Siemens, Erlangen, Germany) was used to obtain echo-planar images (EPI) with blood oxygenation level dependent (BOLD) contrast. The subject's head was fixed with foam pads to minimize head movements. During the scanning procedure, pictures were presented by projection on a screen at the back end of the scanner, which could be seen through a mirror mounted above the subject's head. For functional MRI, an echo planar imaging sequence (interpulse interval or TR = 3.306 s, time to echo or TE = 45ms, flip angle = 90º) was used creating transversal whole brain acquisitions (38 slices, 3 x 3 mm in-plane resolution, slice thickness 2.5 mm with a 0.5 mm inter-slice gap). Two series of pictures were presented (software: E-Prime) in a block design, depicting food or non-food items such as landscapes, people, and houses. These pictures were visually matched for visual complexity, both for the objects shown and their background. They were not systematically matched for color. The pictures were not selected from the IAPS set so that independent ratings for valence/arousal were not available. For the encoding phase 48 pictures and for the retrieval phase 96 pictures (half new, half already seen during the encoding phase) were presented randomly selected for food (half) and nonfood (half). Each picture was displayed for 4 seconds, followed by a pause of 2 seconds before the next picture was shown. A button box was used to

register the subject's response and reaction times. The subjects were not asked to memorize the pictures, but were requested to press the button (yes or no) whether the pictures were taken indoor or outdoor to control for attention differences. During retrieval, subjects performed a two-choice recognition task (seen before/new). 96 fMRI volumes were collected in the encoding phase, whereas during retrieval 176 volumes were acquired. Between the encoding and retrieval subsessions, a T1-weighted structural MRI scan (MP-RAGE, magnetization prepared rapid acquisition gradient echo, resolution 1mm in-plane, 160 slices) was obtained.

Image Processing and Analysis

Statistical Parametric Mapping (SPM5) software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London UK) was used for imaging analysis. The images were realigned to compensate for subject movement and were corrected for differences in slice acquisition timing. The T1-weighted anatomical images obtained from each subject were thereafter coregistered to the mean echo planar images (EPI). Spatial normalization was performed to match a standard template, and images were spatially smoothed using a 6 mm Full Width at Half Maximum (FWHM) filter. Next, imaging data were analysed within the context of the General Linear Model, using boxcar regressors convolved with a synthetic haemodynamic response function. For each subject, we performed food *vs* non-food comparisons and entered the resulting contrast images into second-level (random effects analyses). For main effects (food *vs* non-food) results were thresholded at p<0.05 corrected for multiple comparisons using the False Discovery Rate (FDR) method [27], unless indicated otherwise. Stimulus x condition interaction effects are reported at p<0.001 uncorrected masked with the relevant main effect. Additionally, analyses of covariance were performed using hormone measurements as regressors. Anatomical regions as identified by Montreal Neurological Institute (MNI) coordinates for peak effects were verified using a standard brain atlas.

Biochemical Measurements

Serum leptin and ghrelin were measured with a radio-immunoassay (Linco Research Inc, St. Charles, Missouri, USA). The intra-assay coefficient of variation (CV) for leptin was 3% at 25 ng/ml and 8% at 5 ng/ml and the inter-assay CV was 4% at 25 ng/ml and 8% at 5 ng/ml. For ghrelin the intra-assay CV was 5% at 3000 ng/l, 8% at 2000 ng/l and 10% at 1000 ng/l and the inter-assay CV was 5%. Insulin was measured using the Immunoradiometric assay Biosource/Medgenix Diagnostics, Fleurus, Belgium. The intra-assay CV is 2% at 318 pmol/l and 5% at 40 pmol/l and inter-assay CV 6%. Serum concentrations of glucose were measured with Hexokinase method (Roche diagnostics, Mannheim, Germany) with the inter-assay CV of <2% at the mean values of 4.7 and 18.3 mmol/l. Triglycerides were measured with the Enzymatic colorimetric assay (Roche diagnostics, Mannheim, Germany). The inter-assay CV was <4% at 1 mmol/l and <3% at 2 mmol/l. FFA were measured with an enzymatic colorimetric test (ELAN, Merck, Darmstadt, Germany), the inter-assay CV was <4.5% at 0.73 mmol/l and <4% at 1.02 mmol/l.

Statistical Analysis

Laboratory measurements were analyzed using a standard statistical package (SPSS version 13; SPSS, Chicago, IL, USA). Paired T-tests were used to evaluate changes between the fasting and the satiated state. In addition, Pearson's correlations (one-tailed or two-tailed, depending on specific hypotheses) were calculated between the subscales of the Hunger questionnaire and blood sample parameters as well as the correlations between imaging and laboratory data. Correlations were computed separately for the hungry and satiated conditions.

RESULTS

Psychometric Measurements

To determine the effects of conditions satiated-food, satiated-nonfood and fasting-food, fasting-nonfood on reaction time (RT) and number of correct responses two separate repeated-measures analyses of variance (ANOVA) were used with RT and number of correct responses under each condition as repeated measurements factor. Only RTs for correct trials were evaluated. With respect to RT, within-subjects contrasts indicated that the RT was significantly longer for fasting-food than for fasting-nonfood items (F $(1,14) = 25.22$, $p < 0.0005$, $\eta^2 = 0.64$). In addition, RTs were significantly longer for satiated-food than for satiated-nonfood items (F $(1,14) = 46.90$, $p < 0.0005$, $\eta^2 = 0.77$). There were neither significant differences between the RTs under the fasting and satiated conditions separately analysed for the food and non-food conditions, nor for those averaged across food and non-food conditions.

Furthermore, within-subjects contrasts indicated that the number of correct responses was significantly lower for fasting-food than for fasting-nonfood items (F $(1,15) = 4.56$, $p = 0.05$, $\eta^2 = 0.23$). In addition, there was neither any significant difference between the number of correct responses under the fasting and satiated conditions separately analyzed for the food and non-food condition nor for those averaged across food and non-food conditions.

Laboratory Measurements

Mean glucose levels did not differ between the fasting and satiated state in this study population. As expected, during fasting mean levels of ghrelin and FFA were significantly higher compared to the satiated state. During the satiated state, insulin and triglyceride levels were higher than during the fasting state. Leptin levels were also slightly higher during satiation (Table **1**).

Table 1.   Laboratory Measurements in Healthy Men During Fasting and Satiated Conditions presented as Mean Levels with Standard Deviation

Glucose (mmol/l)	4.79 ± 0.30	4.57 ± 0.33
Triglycerides (mmol/l)	0.77 ± 0.33	1.35 ± 0.57**
Free fatty acids (mmol/l)	0.31 ± 0.11	0.15 ± 0.11**
Insulin (pmol/l)	46.8 ± 21.5	245.7 ± 127.3**
Leptin (ng/ml)	3.0 ± 1.5	3.5 ± 2.1*
Ghrelin (ng/l)	1826.7 ± 402	1386.9 ± 223.8**

* p < 0.05, ** p < 0.01.

Imaging Data

Results of imaging data are summarized in Table **2**. During encoding main effects for food related stimuli *vs* non-food related stimuli were observed in the left fusiform gyrus and the right anterior and posterior hippocampus during the fasting state, and the occipital gyrus bilaterally. Amygdala activity only approached significance. During retrieval there was significant activation in the fusiform gyrus and occipital gyrus bilaterally and the right medial frontal cortex. The right anterior hippocampus approached significance during the satiated state. Interaction effects (increased activation of food *vs* non-food pictures during the fasting compared to the satiated condition) were observed during encoding in right occipital cortex and bilateral fusiform gyrus and amygdala (Table **3**). During retrieval there was more activation during the satiated condition compared to the fasting state in the left fusiform gyrus and occipital cortex.

Correlations Between Imaging and Laboratory Data

During the satiated condition a strong negative correlation was found between leptin levels and activation of the left hippocampus (x=-21, y=-21, z=-9 peak Z score:5.09) and activation of the right insula (x=33, y=18, z=-3 peak Z score:4.74) (Fig. **1**). There was a negative correlation between leptin levels and the temporal lobe bilaterally (x=-57, y=-60, z=-3 peak Z score:4.7 and x=66, y=-33, z=9 peak Z score:3.93 respectively) as well as the frontal gyrus (x=27, y=48, z=9 peak Z score:3.90).

During the fasting condition there was a positive correlation between ghrelin levels and activation of the right and left insula, posterior OFC, left thalamus and right hippocampus but these correlations did not reach significance.

Correlations Between Appetite Assessment Score and Laboratory Data

Under the fasting condition, a significant correlation was found between ghrelin levels and 'thought of food' scale scores ($r = 0.48$, $p = 0.04$, one-tailed). In addition, higher ghrelin concentrations were related to lower insulin concentrations ($r = - 0.55$, $p = 0.035$, two-tailed). Finally, glucose correlated positively with insulin ($r = 0.54$, $p = 0.047$, two-tailed) and with leptin ($r = 0.60$, $p = 0.02$, two-tailed).

With respect to the satiated condition, ghrelin concentrations correlated negatively with scores on the 'eagerness to eat' scale ($r = - 0.61$, $p = 0.008$). Finally, ghrelin correlated negatively with insulin ($r = - 0.58$, $p = 0.02$, two-tailed) and glucose correlated positively with triglycerides ($r = 0.66$, $p < 0.007$, two-tailed).

DISCUSSION

In the present study we investigated the effects of processing visual food *vs* non-food stimuli on brain activation during standardized fasting and satiated conditions. In order to mimic a physiological fasting state in the brain, we adopted a 12-hour fasting period, rather than an

Table 2. **Regions Showing an Increase in Brain Activity (Blood Oxygen Level Dependent Contrasts) in Response to Visual Food Versus Non Food Stimuli**

	Left/Right	Fasting+Satiated				Fasting				Satiated			
		x	y	z	Peak Z	x	y	z	Peak Z	x	y	z	Peak Z
Encoding													
Amygdala	L	-18	-9	-21	2.89b)	-18	0	-12	3.07a)				
	R					33	0	-24	2.92b)				
Anterior hippocampus	R					30	-12	-24	2.61b)				
Posterior hippocampus	R					30	-24	-6	2.58b)				
Fusiform gyrus	L					-36	-84	-12	4.20				
	R	36	-51	-18	4.50a)	30	-84	3	4.52				
Occipital cortex	L	-36	-84	-12	4.06a)	-36	-84	-12	4.20				
	R	39	-75	-9	3.90a)	42	-54	-18	4.42				
Retrieval													
Anterior hippocampus	R	33	-9	-27	2.71b)					36	-12	-24	3.02b)
Fusiform gyrus	L	-45	-57	-21	4.28	-45	-57	-21	3.13a)	-30	-75	-12	4.94
	R	36	-63	-15	4.00	45	-45	-18	3.56a)	30	-72	-6	4.24
Occipital cortex	L	-33	-81	-9	4.76	-33	-81	-9	3.75a)	-27	-81	-12	4.45
	R	33	-75	-15	3.84	33	-75	15	3.22a)	18	-90	-9	3.45
Medial frontal cortex	R	3	51	9	3.32	3	51	9	3.52a)				

x, y, z = coordinates of peak voxel from the Montreal Neurological Institute (MNI) brain peak Z = standardized significant value.
Main effects significant corrected for multiple comparisons (False Discovery Rate method) unless indicated otherwise
a) P uncorrected <0.001
b) P uncorrected <0.005

Table 3.   Regions Showing Group Interactions in Response to Visual Food Versus Non Food Stimuli

	Left/Right	Fasting>Satiated				Satiated>Fasting			
		x	y	z	Peak Z	x	y	z	Peak Z
Encoding									
Amygdala	L	-18	-6	-24	2.66				
	R	33	0	-24	2.74				
Fusiform gyrus	L	-33	-84	-6	3.25				
		-45	-60	-6	3.38				
	R	42	-54	-18	3.55				
Occipital cortex	R	30	-84	3	4.73				
Retrieval									
Fusiform gyrus	L					-27	-75	-12	3.42
Occipital cortex	L					-12	-90	-6	3.58

x, y, z = coordinates of peak voxel from the Montreal Neurological Institute (MNI) brain peak Z = standardized significant value.
Main effects significant corrected for multiple comparisons (False Discovery Rate method) unless indicated otherwise.
P <0.001.

extremely long fasting period as used by others [28]. Also, we performed a second measurement one hour after ingestion of a standardized meal, expecting the acute metabolic and hormonal changes following a meal to be effective in producing a satiated state. Functional MRI sessions were performed in balanced order, with a one-week interval to separate the two conditions (fasting and satiated) to control for order effects. Main effects of food *vs* non-food stimuli were observed during encoding in the ventral visual stream, including fusiform gyrus and parahippocampal areas bilaterally, although hippocampus and amygdala were only found at a lower threshold. Given the fact that food and non-food pictures were matched for visual complexity, these effects are likely to be due to increased salience of food pictures, in particular when subjects were hungry. These results are in accordance with previous reports investigating visual processing of food stimuli using fMRI [10,29]. In addition to the medial temporal regions observed in the present study, the orbitofrontal cortex has been demonstrated to be involved in feeding related behaviour both in animals and humans [23,30,31]. In our study, amygdala activity was observed for food *vs* non-food pictures and interaction analyses showed that amygdala activity was increased in the fasting state as expected. Due to susceptibility artefacts (signal loss due to the presence of bone-air transitions, in particular nasal sinuses) we were not able to adequately measure BOLD activation in the medial OFC; also, ventral striatum activity was not found even though the ventral striatum is likely to be involved in signalling rewarding properties of food [25]. For this reason, some researchers have used ^{15}O-PET rather than fMRI when investigating OFC function [31-33]. In addition, detecting amygdala activity may be problematic due to rapid habituation [10].

During the two conditions of fasting and satiation, mean reaction time for food pictures was longer than for non-food pictures. Also, memory performance for food-pictures was lower than for non-food pictures. The latter finding was somewhat unexpected given the association between salience and memory performance for food stimuli as reported by

others [9], although we suggest that this could be due to greater semantic cohesion of the food stimuli [34] relative to nonfood stimuli.

Previous research has demonstrated that the gut-brain axis and various hypothalamic factors are of importance in regulating the energy balance and the perception of hunger and satiety [15,35-37]. In the present study, we found a positive correlation between ghrelin and food-related activation in the insula areas bilaterally, as well as in the right hippocampus, during the fasting state although these associations did not reach significance. As ghrelin is the only orexigenic hormone [38,39] this association would be expected. Also, it is known to stimulate meal initiation, and receptors for ghrelin have been located in the hippocampus, arcuate nucleus and ventromedial hypothalamus. When correlating the hunger scores with ghrelin we found a positive correlation between ghrelin and "thought of food" hunger scores, consistent with the findings of others [13].

In the satiated condition, there was a strong negative correlation between leptin and left hippocampus and right insula activity. Thus, high leptin levels correlated with a lowered response to food related pictures. The insula has been implicated in multiple processes, including interoceptive awareness of body states, food craving, and basic emotions. Hippocampal activation is typically increased during memory processes (registration of new information and retrieval), and our data indicate that high levels of leptin are associated with a blunted response. Stimulation of the hypothalamus by leptin results in the suppression of food intake, stimulation of satiated behaviour, and energy expenditure [40-43]. Also, in obese subjects, correlations have recently been reported between leptin and regional grey matter volumes [44].

In the present study, we did not find significant correlations between insulin and activation of limbic areas during the fasting state as might be expected. Nevertheless, interpretations of the correlations between insulin and regional brain activation areas are not straightforward as
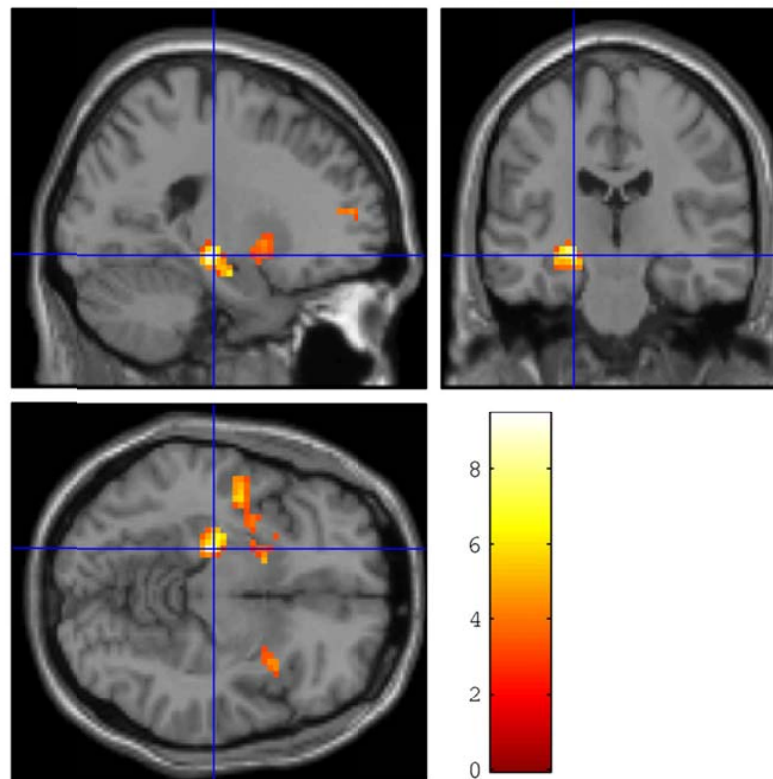
Fig. (1). The negative correlation between leptin levels and activation of the left hippocampus for the food *vs* non-food contrast. Colour bar shows statistical T-values. See text for details.

insulin signalling in the brain is highly complex, sharing common pathways with leptin and serotonin [45,46].

In contrast to the findings of Gautier *et al*, we did not find correlations between postprandial FFA and activation in hippocampal and parahippocampal regions [28]. Also, there were no significant correlations between glucose and the activation in the limbic system during the fasting and satiated condition when viewing food *vs* nonfood food pictures.

Our study has several potential limitations. The sample size was only moderate, although sample sizes of 12-15 are customary in fMRI studies. Lately it has been shown to be of importance to categorize the visual food stimuli in low versus high calorie stimuli as this could influence the results especially during the fasting state [47]. Also, recently published data have implicated adiponectin in regulating food intake and energy expenditure [48,49]. Moreover, glucagon-like peptide-1 (GLP-1), which is synthesized in the brain as well [50,51], may also be involved. Therefore, future research should attempt to investigate the correlations between these hormones/adipokines and regional brain activation using a similar fMRI paradigm.

Finally, various local regulatory circuits and locally produced/derived adipokines are presumably involved in the processing of food intake regulation and appetite, but such factors are as yet difficult to assess. This regulation is likely to be highly complex, involving the dopaminergic system, and psychosocial factors including stress [52-55].

In summary, in the present study, main effects of food versus non-food visual stimuli during encoding were observed in the ventral visual stream, including fusiform gyrus and hippocampal areas and occipital cortex bilaterally, and at lower threshold the amygdala areas. There was significantly more activation in the fusiform and hippocampus gyrus bilaterally during the fasting condition when compared to the satiation state, most likely due to increased salience of food pictures. Furthermore, there was a strong negative correlation between leptin and left hippocampus and right insula activity when the subjects were satiated.

Further insights in the neural correlates of processing food stimuli in obesity, binge eating and anorexia nervosa will be of importance in the search for individualized treatment such as behavioural counselling and in the search for effective drug treatments.

CONFLICT OF INTEREST

Declared none.

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