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CHAPTER 6

Emotional eating is associated with increased brain responses to food-cues and reduced sensitivity to GLP-1 receptor activation



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ABSTRACT

Objective

The neural correlates and pathophysiology of emotional eating are insufficiently known. Glucagon-like peptide-1 (GLP-1), a post-prandial hormone, plays a role in feeding behaviour by signalling satiety to the brain. GLP-1 receptor agonists, used for treatment of type 2 diabetes (T2DM), promote weight loss. This study investigated the association between emotional eating and responses to food-cues in brain areas involved in satiety and reward processing, and GLP-1 receptor agonist-induced effects on these brain responses.

Methods

T2DM patients with obesity, normoglycaemic individuals with obesity and lean individuals (n=48) were studied in a randomised placebo-controlled cross-over study. Using functional MRI, we determined the relation between emotional eating and regional brain responses to visual food stimuli, and acute effects of intravenous administration of the GLP-1 receptor agonist exenatide on these responses.

Results

Emotional eating scores positively correlated with responses to food-cues in lean subjects in the insula, in normoglycaemic subjects with obesity in the insula and in T2DM patients in the amygdala, orbitofrontal cortex and insula. Emotional eating scores negatively correlated with exenatide-induced reductions in responses to food-cues in normoglycaemic subjects with obesity in amygdala and in T2DM patients in insula.

Conclusions

Our findings indicate that emotional eaters have altered brain responses to food-cues and are less sensitive to the central effects of GLP-1 receptor activation.

INTRODUCTION

The increasing prevalence of obesity is related to recent environmental changes, including increased access to palatable high calorie foods. However, not all individuals become obese. Some individuals can control their food intake and maintain a neutral energy balance while others cannot. Food intake is driven by homeostatic and non-homeostatic factors (1). Homeostatic feeding controls energy balance by adjusting food intake to energy needs. This balance is regulated in a complex manner by several peripheral signals, such as feeding-related hormones (i.e. insulin, ghrelin, leptin and glucagon-like peptide-1 (GLP-1)), which relay information on hunger and satiety to the brain (2;3). However, non-homeostatic or hedonic factors can override this homeostatic pathway which may result in overeating. Stress, negative moods and emotions can stimulate eating even in absence of energy needs. Emotional eating, a tendency to eat in response to negative emotions, is associated with obesity (4;5), with less weight loss during a weight loss program as well as following bariatric surgery (6). In addition, emotional eating is associated with weight regain after weight loss accomplished by treatment interventions (7). However, the neural correlates and pathophysiological mechanisms of emotional eating are insufficiently known. Glucagon-like peptide-1, a postprandial gut-derived hormone, plays an important role in the regulation of feeding behaviour by signalling satiety to the brain (8). Furthermore, animal data showed that GLP-1 receptor activation decreases motivated behaviour for a food reward by interacting with the mesolimbic system (9). GLP-1 receptor agonists, currently used for the treatment of type 2 diabetes mellitus (T2DM), stimulate insulin secretion and inhibit glucagon release. In addition, GLP-1 receptor agonists were shown to increase satiety and to reduce food intake, resulting in body weight loss (10;11). However, weight loss is only seen in a subset of patients (12). It is unclear why some patients respond with weight loss and others do not.

We previously demonstrated, using functional MRI (fMRI), that T2DM patients with obesity and normoglycaemic subjects with obesity have increased responses to food pictures in appetite- and reward-related brain regions and that GLP-1 receptor activation blunts these hyperactivations (13). In the current report, we hypothesised that emotional eating is associated with regional brain responses to food pictures and with the GLP-1 receptor agonist-induced effects on these responses. Therefore, we investigated the association of emotional eating, as assessed by the Dutch Eating Behaviour Questionnaire (DEBQ)(4), with blood oxygen level dependent (BOLD) responses to food pictures during fMRI, and the GLP-1 receptor agonist-induced reductions in these BOLD responses. We also determined the association between emotional eating and GLP-1 receptor agonist-induced changes in food intake during an ad libitum lunch buffet after the fMRI session.

METHODS

Participants

This study, part of a larger study (NCT01281228) (13), was approved by the Medical Ethics Committee of the VU University Medical Center and was performed in accordance with the Helsinki Declaration. Effects of GLP-1 receptor activation on brain responses to visual food cues in the same population studied in this paper were described previously (13). All participants provided written informed consent before participation. We included 16 T2DM patients with obesity, 16 normoglycaemic individuals with obesity and 16 healthy lean individuals, matched for gender and age. Inclusion and exclusion criteria were reported previously (13). In short, inclusion criteria were age range 40-70 years, Caucasian ethnicity, right-handedness and stable body weight (in kilograms) defined as < 5% reported change during the previous 3 months. Other inclusion criteria included body mass index (BMI) > 30 kg/m² for individuals with obesity and T2DM patients, BMI < 25 kg/m² for lean controls, normoglycaemia for individuals with obesity and lean controls as defined by fasting plasma glucose < 5.6 mmol/l and 2-hour glucose < 7.8 mmol/l following a 75g oral glucose tolerance test (OGTT). For T2DM patients, HbA1c had to be 6.0-8.5% during treatment with metformin and/or sulphonylurea derivative. To determine the effects of emotional eating in the normal range, we excluded individuals with eating disorders (assessed by the Eating Disorder Inventory II) (14). Other exclusion criteria were a history of cardiovascular, renal and liver disease, malignancies, neurological and psychiatric disorders including depression (assessed by Center for Epidemiologic Studies Depression scale) (15). Twelve T2DM patients and 3 individuals with obesity used antihypertensive medication, 13 T2DM patients and 1 individual with obesity used statins. In the T2DM group, 8 participants were treated with metformin monotherapy and 8 used metformin in combination with a sulphonylurea. The lean controls did not use any medication.

Experimental design

The study was a randomised, placebo-controlled, crossover study. The design of the study was described in detail previously (13). In short, subjects received intravenous infusion of the GLP-1 receptor agonist exenatide or placebo in random order during two separate test days. In order to prevent exenatide-induced changes in glucometabolic parameters, all measurements were performed during somatostatin pancreatic-pituitary clamps. Somatostatin (Somatostatin; Eumedica) was infused at a rate of 60 ng/kg/min to suppress endogenous insulin, glucagon, growth hormone and GLP-1 production. Human glucagon (0.6ng/kg/min; Glucagen; Novo Nordisk), growth hormone (2ng/kg/min; Genotropin; Pfizer) and insulin (0.6mU/kg/min; Actrapid; Novo Nordisk) were infused at constant rates to achieve stable levels. Glucose (200 g/l) was infused at a variable rate to clamp plasma glucose at 5.0 mmol/l. Intravenous exenatide (Byetta; Eli Lilly) or

placebo infusion was started 60 minutes after the start of the clamp at an infusion rate of 50 ng/min for 30 minutes, and was decreased to 25 ng/min for the remaining time of the clamp procedure (16). Plasma glucose was measured every 10 minutes. All visits commenced at 8:30 AM after an overnight fast and participants did not exercise or drink alcohol for 24 h before the sessions.

fMRI paradigm

During the fMRI task participants watched 126 pictures within three categories: high calorie food (sweet and savory), low calorie food (fruit and vegetables) and neutral non-food items (trees, rocks, flowers etc). The design was adapted from previous studies (17;18). Pictures were presented in a block design format, with a total of 3 runs. Within each run there were 6 blocks of pictures: 2 blocks of high calorie foods, 2 blocks of low calorie foods and 2 blocks of non-food pictures (Figure 1). In each block of 21 seconds, 7 individual pictures were presented for 2.5 seconds each followed by a 0.5 second gap each. Each block was followed by 9 seconds of grey blank screen with a fixation cross. Across each block and session pictures were matched for shape and colour. Participants were instructed to watch all pictures and to try to remember them for a recognition test. Participants were given a recognition test after all measurements, consisting of 20 laminated pictures (10 pictures of the MRI task and 10 novel pictures) and had to indicate whether they had seen the picture during the task or not.

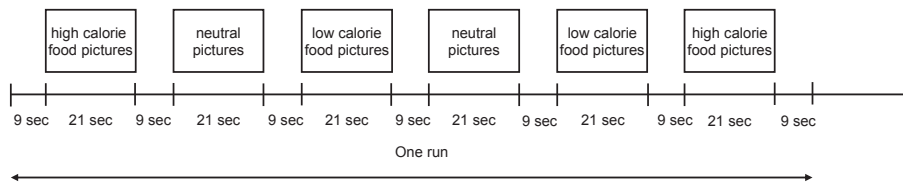


Figure 1 | fMRI paradigm

One of the 3 runs within 1 fMRI session. In each run 6 blocks of 7 pictures were viewed, two blocks each of high calorie food, low calorie food and neutral pictures. The blocks were separated by 9 seconds of grey blank screen with a fixation cross. The order of blocks was randomised with the constraint that a given picture category was not followed by the same category.

Image acquisition and analysis

MRI data were acquired on a 3.0 Tesla GE Signa HDxt scanner (General Electric, Milwaukee, Wisconsin, USA). MRI acquisition and analyses were used as described previously (13) Functional images were analysed with SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK). The origin of each MR volume was aligned to the anterior commissure. Series were corrected for differences in slice acquisition times and were realigned to the first volume. T1-coregistered volumes were normalised to Montreal Neurological Institute (MNI) space, resliced to 3 x 3 x 3 mm voxels and spatially smoothed using an 8 mm full width at half

maximum Gaussian kernel. After high-pass filtering (cut-off 128 seconds i.e. 0.0078 Hz) to remove low-frequency noise, functional scans were analysed in the context of the general linear model. At the first level each block of pictures was modelled using boxcar functions convolved with a canonical haemodynamic response function. For each subject and for each condition, contrast images were computed (food pictures vs. non-food pictures; high-calorie food pictures vs. non-food pictures). To determine whether neuronal responses were related to emotional eating scores, first-level contrast images were entered into second level regression analyses. Individual maps were furthermore created assessing change in neural activation between the different scan days (placebo vs. exenatide) for these contrasts, and emotional eating was regressed on change in neural response. All analyses were corrected for BMI, by adding BMI as covariate of no interest. T-maps were initially thresholded for display at $P(\text{uncorrected}) = 0.005$, with a cluster size threshold of 5 voxels. A priori regions of interest (ROI) were determined based on previous studies i.e. insula, putamen, caudate nucleus, amygdala and OFC (17;19;20). Only brain activations that survived family-wise error (FWE) correction for multiple comparisons ($P(\text{FWE}) < 0.05$) at the voxel level within the ROIs using a small volume correction (SVC), or across the entire brain for regions not a priori of interest, are reported. SVC was performed using 5 mm (for amygdala) or 10 mm (for insula, putamen, caudate nucleus and OFC) radius spheres (21-24).

Questionnaires

All participants filled in the Dutch Eating Behaviour Questionnaire-Emotional Eating subscale (4) during a screening visit. The scale consists of 13 questions assessing the frequency of eating in response to various negative emotions (e.g. "Do you have the desire to eat when you feel irritated?", "Do you have the desire to eat when you feel lonely?"). All items were rated on a five-point scale ranging from 1 (never) to 5 (very often). The scale has demonstrated good internal consistency (Cronbach's $\alpha=0.86-0.97$)(4). In the present study, α was 0.96.

***Ad libitum* lunch buffet**

After the MRI session, participants were presented a choice buffet to assess energy intake, as described previously (13;25). The choice buffet consisted of wholemeal bread (4 slices), white bread (4 slices), ham (2 slices), chicken (2 slices), cheese (2 slices), margarine (3 cups), mayonnaise (20 ml), marmalade (2 cups), peanut butter (2 cups), sliced tomato and cucumber, lettuce, strawberry yoghurt, apple, banana, orange juice, coffee, tea, chocolate muffin, cake. Participants were advised to eat as much as they wanted. They were not aware that their choices and food intake were being monitored. After 30 minutes the buffet was taken away and the total kilocalories consumed were calculated based on the food labels and the Dutch Food Composition Table.

Statistical analyses

Clinical group data are expressed as mean \pm SEM (unless otherwise stated) and were analysed with the Statistical Package for the Social Sciences (SPSS) version 20. Between-group differences were analysed with ANOVA (emotional eating score, subject characteristics, caloric intake, recognition test score) or, in case of more than 1 time point (i.e. glucose/glucagon/growth hormone/exenatide levels, glucose infusion rate), with repeated measures ANOVA using time (minutes) as within-subject factor and group as between-subject factor. Within-group differences were analysed using repeated measures ANOVA using treatment and time (minutes) as within-subject factor (caloric intake, glucose/glucagon/growth hormone levels, glucose infusion rate). In case of a significant result, a post-hoc Bonferroni multiple comparisons correction was used. In case of skewed data, Kruskal-Wallis test was used for between-group differences and Friedman test for within-group differences. In case of a significant result Mann-Whitney U-test for between-group analysis or Wilcoxon signed rank for within-group analysis with post-hoc Bonferroni correction was performed. Linear regression was used to examine associations. $P < 0.05$ was considered statistically significant.

RESULTS

Group demographics

All 48 subjects had both the placebo test day and the exenatide test day. Participants in the three groups were age- and gender-matched, T2DM patients and normoglycaemic subjects with obesity were also BMI-matched (Table 1). As expected, there was a significant difference in emotional eating scores between the lean subjects, subjects with obesity and T2DM patients (1.55 ± 0.14 , 2.19 ± 0.18 and 2.04 ± 0.20 , respectively, $p = 0.037$, with the subjects with obesity having a significant higher score compared to the lean subjects (post-hoc $p = 0.043$) (Table 1)). Emotional eating score was positively correlated with BMI ($r = 0.45$; $p = 0.001$).

Blood glucose was successfully clamped at approximately 5.0 mmol/l during the fMRI and *ad libitum* lunch (t=90 until t=180 min). Due to the pancreatic clamp, no significant differences in circulating hormones and metabolites (glucose, insulin, glucagon, growth hormone and non-esterified fatty acids) were found between the different test days, as described in detail previously (13).

Table 1 | Baseline characteristics

	Lean (n=16)	Obese (n=16)	T2DM (n=16)	ANOVA P-value
Age (years)	57.8 ± 1.9	58.0 ± 2.1	61.4 ± 1.5	0.3
Gender, male/female (n)	8/8	8/8	8/8	-
Weight (kg)	71.1 ± 2.7	100.6 ± 2.8*	97.9 ± 3.0*	<0.001
Body mass index (kg/m ²)	23.2 ± 0.4	32.6 ± 0.7*	34.0 ± 0.9*	<0.001
Waist circumference (cm)	85.5 ± 1.9	112.7 ± 2.1*	115.7 ± 1.8*	<0.001
Systolic blood pressure (mmHg)	120 ± 4	127 ± 3	141 ± 3†	<0.001
Diastolic blood pressure (mmHg)	75 ± 2	79 ± 2	83 ± 2*	0.03
Fasting plasma glucose (mmol/l)	5.3 ± 0.1	5.3 ± 0.1	8.4 ± 0.5†	<0.001
Glucose 2h after OGTT (mmol/l)	5.1 ± 0.3	5.5 ± 0.3	-	0.2
HbA1c (%)	5.5 ± 0.03	5.5 ± 0.07	6.9 ± 0.22†	<0.001
HbA1c (mmol/mol)	37.4 ± 0.3	37.5 ± 0.08	51.6 ± 2.4 †	<0.001
Diabetes duration (years)	-	-	7.0 [4.25, 10.75]	-
DEBQ emotional eating score	1.55 ± 0.14	2.19 ± 0.18*	2.04 ± 0.20	0.037

Data are means ± SEM or median [interquartile range].

*Statistically significant different from lean (post-hoc Bonferroni corrected $P < 0.05$)

†Statistically significant different from lean and obese (post-hoc Bonferroni corrected $P < 0.05$)

OGTT, oral glucose tolerance test; T2DM, type 2 diabetes patients

Association between emotional eating and brain responses to food pictures

Emotional eating scores were positively correlated with brain responses to food vs. non-food pictures in the placebo condition in normoglycaemic subjects with obesity in right insula and in T2DM patients in bilateral amygdala, bilateral inferior OFC and right insula, but not in lean subjects (Table 2; Figure 2). Emotional eating scores were also positively correlated with brain responses to high-calorie food vs. non-food pictures, i.e. in lean subjects in left insula, in subjects with obesity in right insula and in T2DM patients in right inferior OFC (Table 2). All analyses were corrected for BMI since emotional eating scores have been shown to correlate with BMI (4). Without adjustment for BMI, the positive associations between emotional eating and food-related brain responses were comparable, but an additional association of emotional eating with food-related brain responses in the amygdala was present without adjustment for BMI in patients with T2DM (high calorie vs. non-food) (data not shown).

Table 2 | Association between emotional eating scores and brain responses to food pictures

Group	Region	Side	Cluster	B	T-value	p _{uncor}	p _{FWE}	MNI (x, y, z)
Lean								
Food vs non-food	-							
High-cal vs non-food	Insula	L	5	+0.19	3.89	0.001	0.035	-33,17,7
Obese								
Food vs non-food	Insula	R	34	+0.49	4.48	<0.001	0.014	36,32,4
High-cal vs non-food	Insula	R	22	+0.19	4.24	<0.001	0.024	33,32,4
T2DM								
Food vs non-food	Inferior OFC	L	16	+0.34	7.17	<0.001	<0.001	-39,26,-17
	Amygdala	R	62	+0.46	6.13	<0.001	<0.001	24,5,-17
	Insula	R	62	+0.41	4.71	<0.001	0.016	27,14,-20
	Inferior OFC	R	7	+0.27	4.40	<0.001	0.024	27,32,-17
	Amygdala	L	28	+0.40	4.22	<0.001	0.001	-30,2,-20
High-cal vs non-food	Inferior OFC	L	10	+0.21	4.21	0.001	0.033	-39,29,-17

B, regression coefficient after adjustment for BMI; T, t-value; p_{uncor}, p-value uncorrected for multiple comparisons; p_{FWE}, p-value Family-Wise Error corrected for multiple comparisons on the basis of cluster extent (small volume correction); R, right; L, left; MNI, Montreal Neurological Institute coordinates in mm; Cal, calorie.

Association between emotional eating and exenatide-induced effects on brain responses to food pictures

The infusion of exenatide (approved for subcutaneous use in clinical practice) resulted in pharmacologically relevant plasma concentrations with no statistically significant differences between the lean subjects, subjects with obesity and T2DM patients (181 ± 13 , 154 ± 13 and 153 ± 13 pg/ml respectively, $p = 0.25$) (26;27).

We previously described that exenatide vs. placebo reduces responses to food pictures in subjects with obesity and T2DM patients (in insula, amygdala, putamen and OFC), but not in lean subjects (13). In the current analyses, we found that emotional eating scores were negatively correlated with these exenatide-induced reductions in responses to food vs. non-food pictures, i.e., in normoglycaemic subjects with obesity in bilateral amygdala and in T2DM patients in right insula (Table 3; Figure 3). The negative associations between emotional eating and exenatide-induced changes in food-related brain responses were comparable with and without adjustment for BMI in T2DM patients, but the negative association of emotional eating with exenatide-induced changes in brain responses in the amygdala in obese individuals ceased to be significant without adjustment for BMI (food vs. non-food) (data not shown).

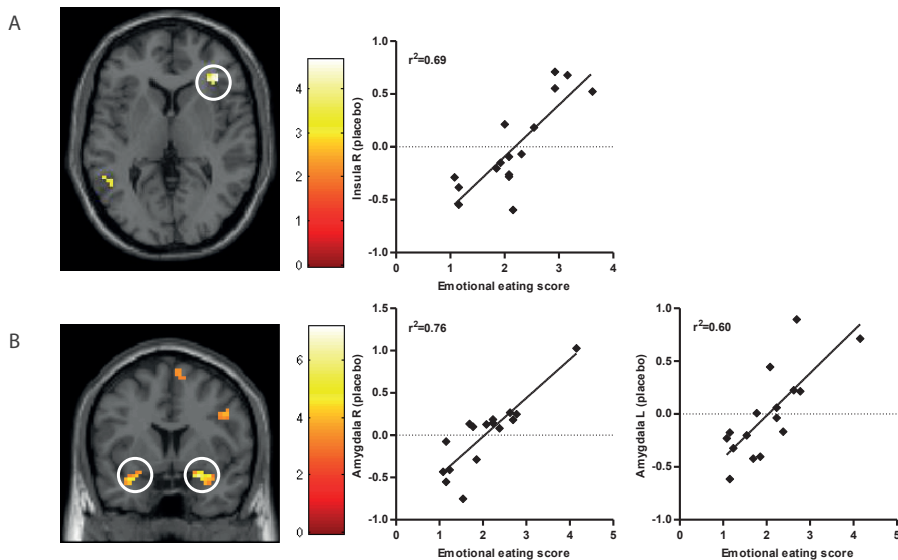


Figure 2 | Association between emotional eating and brain responses to food pictures

A | axial brain slice showing positive correlation in subjects with obesity in right insula between emotional eating and brain responses to food vs. non-food pictures;

B | coronal brain slice showing positive correlation in T2DM patients with obesity in left and right amygdala between emotional eating and brain responses to food vs. non-food pictures.

Left side of the slices is the left side of the brain. The colour scale reflects the T-value of the functional activity. Results are presented at a threshold of $P < 0.05$, FWE corrected on the basis of cluster extent. In the graphs on the right the BOLD signal intensity (arbitrary units) is plotted as a function of emotional eating score.

As expected, there was no correlation between emotional eating scores and exenatide-induced reductions in regional brain responses to food pictures in lean subjects. There were no significant correlations between emotional eating and exenatide-induced changes in brain responses to high-calorie food-pictures vs. non-food pictures.

A recognition test was performed after all measurements to ensure that the subjects watched the pictures attentively during the fMRI session. There were no significant differences in recognition test scores between groups and between sessions (data not shown). In addition, recognition test scores did not correlate with emotional eating score.

Association between emotional eating and exenatide-induced reductions in caloric intake

There was no significant correlation between emotional eating and *ad libitum* intake during the lunch buffet in the placebo condition in each group. Although we observed that exenatide vs. placebo reduced caloric intake as described previously (13), we found no correlation between these exenatide-induced changes in caloric intake and emotional eating scores.

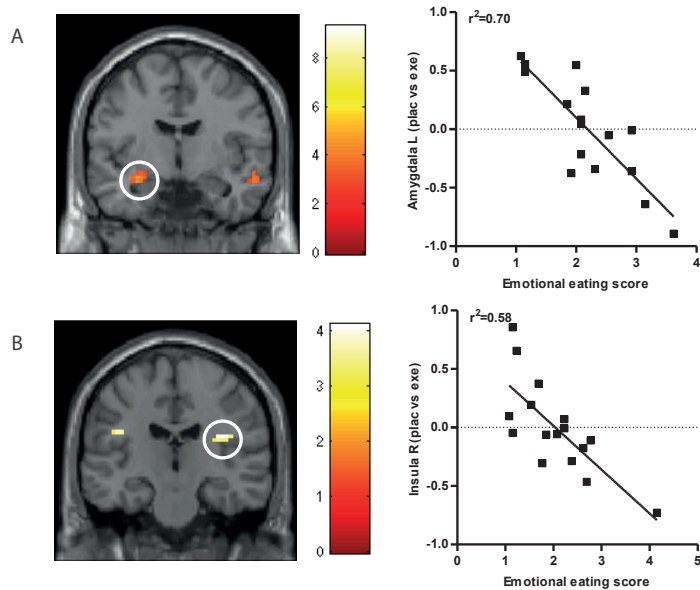


Figure 3 | Association between emotional eating and exenatide-induced reductions in brain responses to food pictures

A | coronal brain slice showing negative correlation in subjects with obesity in left amygdala between emotional eating and exenatide-induced reductions in brain responses to food vs. non-food pictures (placebo vs. exenatide);

B | coronal brain slice showing negative correlation in T2DM patients with obesity in right insula between emotional eating and exenatide-induced reductions in brain responses to food vs. non-food pictures (placebo vs. exenatide).

Left side of the slices is the left side of the brain. The colour scale reflects the T-value of the functional activity. Results are presented at a threshold of $P < 0.05$, FWE corrected on the basis of cluster extent. In the graphs on the right the BOLD signal intensity (arbitrary units) is plotted as a function of emotional eating score. Plac, placebo; exe, exenatide

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Table 3 | Association between emotional eating scores and exenatide induced reductions in brain responses (food vs. non-food)

Group	Region	Side	Cluster	B	T-value	p _{uncor}	p _{FWE}	MNI (x, y, z)
Lean	-							
Obese	Amygdala	L	61	-0.52	4.62	<0.001	0.003	-30,-7,-14
	Amygdala	R	21	-0.79	3.57	0.001	0.009	33,2,-20
T2DM	Insula	R	17	-0.37	4.05	0.001	0.032	36,-19,22

B, regression coefficient after adjustment for BMI; T, t-value; p_{uncor}, p-value uncorrected for multiple comparisons; p_{FWE}, p-value Family-Wise Error corrected for multiple comparisons on the basis of cluster extent (small volume correction); R, right; L, left; MNI, Montreal Neurological Institute coordinates in mm

DISCUSSION

Emotional eating is an important aspect of overeating and may have an important role in the development of obesity. The neural correlates and pathophysiology of emotional eating are however not well delineated. This is the first study to demonstrate that higher emotional eating scores are associated with increased responses while watching food pictures in appetite- and reward-related brain areas in normoglycaemic subjects with obesity, in lean subjects and T2DM patients with obesity. In addition, we found that higher emotional eating scores were associated with less pronounced GLP-1 receptor agonist-induced reductions in regional brain responses to food pictures in subjects with obesity and in T2DM patients only.

Using a well-validated fMRI paradigm (17;18;24), we found a positive correlation between emotional eating scores and responses to food pictures in lean subjects in left insula, in normoglycaemic subjects with obesity in right insula and in T2DM patients in bilateral amygdala, bilateral inferior OFC and right insula. These brain areas have been implicated in the regulation of appetite and in reward processing. The amygdala was shown to play a role in processing positive as well as negative emotions and in stimulus-reward learning (28). The inferior OFC is likewise involved in reward processing and also in decision making (29;30). We found a positive correlation between emotional eating and food-related brain responses in the anterior insula. The anterior insula was shown to be involved in gustatory perception (31), which is represented in the processing of visual food cues (32), tasted or smelled food stimuli (33) and also in food craving (34). Our findings expand findings from a previous study measuring event related potentials (ERP) in healthy young females while watching food pictures. In this study, high emotional eaters compared to low emotional eaters showed enhanced late positive potential over parieto-occipital regions (35). ERPs have a spatial resolution that is much lower than that of fMRI, therefore ERPs are less well suited to research questions about the location of neural activity (36), making their findings difficult to compare with our results. In a previous study that also used fMRI, but with a different paradigm, a relation was found between emotional eating and responses in reward-related brain areas. It was shown that emotional eaters have greater activation of the parahippocampal gyrus and anterior cingulate gyrus during anticipation of chocolate milkshake receipt during a negative mood (37). The differences between these studies and ours are likely to be explained by the different methods used (ERP versus fMRI) and different tasks used (visual food stimuli versus chocolate milk receipt). Thus, it seems that emotional eaters have an increased neural response when anticipating food intake or when viewing visual food cues. It could be speculated that emotional eaters experience increased anticipation of the palatability of a food reward, which may lead to cravings for food. Another theory is that overeating leads to hyperactivation of appetite- and reward-related brain areas

in response to anticipation of palatable food via conditioning (38). Whether increased neural responses to visual food cues are a cause or a consequence of overeating, cannot be determined from our study. Two prospective studies showed that altered brain responses to visual food cues can predict future weight change, suggesting that changes in brain responses to food cues may be causal in the development of changes in food intake (21;39), but future studies are needed to further elucidate this issue.

We found a negative correlation between emotional eating scores and exenatide-induced reductions in responses to food versus non-food pictures in normoglycaemic subjects with obesity in bilateral amygdala and in T2DM patients in right insula. It could be speculated that emotional eaters are less sensitive to physiological signals that regulate satiety, such as GLP-1. This finding may be a mechanistic explanation for the fact that treatment with GLP-1 receptor agonists is only associated with significant body weight loss in a subset of patients (11;12). Further support for a central mechanism underlying the heterogeneity in GLP-1 receptor agonist-induced weight loss comes from an fMRI study in men with obesity, without T2DM. In this study, responders (showing a reduction in energy intake after exenatide vs. placebo infusion) had higher connectedness of the hypothalamus during exenatide infusion in comparison to non-responders (40). We previously demonstrated that exenatide-induced changes in brain responses to food pictures correlate with reductions in subsequent food intake. In our current analyses emotional eating correlated with exenatide-induced changes in brain responses to food pictures, but not with exenatide-induced changes in *ad libitum* food intake. This may be due to the fact that in emotional eaters, an *ad libitum* lunch buffet in an experimental setting is not a good proxy for caloric intake in daily life. Although there was no association between emotional eating and changes in food intake, our data suggest that it is important to investigate the relation between emotional eating and body weight loss in clinical trials with GLP-1 receptor agonists, under normal physiological conditions. Insights in this relation could be clinically relevant for deciding which patients would benefit most from treatment with GLP-1 receptor agonists with respect to body weight loss.

We found no correlation between emotional eating and exenatide-induced changes in brain responses to high-calorie vs. non-food pictures. In this analysis, only the high-calorie food pictures are analysed instead of all food pictures (high- and low-calorie), which may result in decreased power. This may result in a reduced likelihood to determine correlations with emotional eating. In the lean subjects we did not find a correlation between emotional eating and exenatide-induced effects on regional brain responses to food pictures. This may have been caused by the fact that lean subjects show lower activations in response to watching food pictures per se, which may impede the possibility to find significant correlations.

A limitation of our study is that the groups were relatively small. We could not combine groups to enlarge sample size because we previously demonstrated that brain responses to food pictures and exenatide-induced effects on these responses differ between groups (13). However, even with these small groups we found significant correlations in all groups.

In summary, we found that emotional eating is positively related to brain responses to food pictures in normoglycaemic subjects with obesity and T2DM patients with obesity. In addition, we found a negative correlation between emotional eating and exenatide-induced reductions in brain responses to food pictures. Our findings suggest that emotional eaters have stronger brain responses to watching food pictures and are less sensitive to the effects of GLP-1 receptor activation on these brain responses. Insights into the neural correlates and pathophysiology of emotional eating may help to develop new treatment strategies for obesity and to select patient groups for treatment with GLP-1 receptor agonists.

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