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ORIGINAL ARTICLE

Changes in brain activity after weight loss

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Summary

Objectives

The importance of the regulatory role of the brain in directing glucose homeostasis, energy homeostasis, eating behaviour, weight control and obesity is increasingly recognized. Brain activity in (sub)cortical neuronal networks involved in homeostatic control and hedonic responses is generally increased in persons with obesity. Currently, it is not known if these functional changes can be affected by dieting. The aim of the current study was to investigate whether prolonged fasting and/or weight loss influences neuronal brain activity in obese persons.

Methods

Fourteen participants with obesity were included (two male participants and 12 female participants, body mass index 35.2 ± 1.2 kg m^{-2}). Whole-brain resting-state functional magnetic resonance imaging was performed after an overnight fast, after a prolonged 48-h fast and after an 8-week weight loss intervention.

Results

An 8-week weight loss intervention decreased BOLD signal in areas of the brain involved in salience, sensory motor and executive control. BOLD signal in these areas correlated with leptin levels and body mass index.

Conclusions

Weight loss decreased activity in brain areas involved in feeding behaviour and reward processing. These results indicate that these obesity-associated alterations in neuronal activity are related to excessive body weight and might change after weight loss.

Keywords: Diet intervention, functional brain responses, obesity, weight loss.

Introduction

The importance of the regulatory role of the brain in directing energy homeostasis, eating behaviour, weight control and thus obesity is increasingly recognized (1–3). Energy homeostasis is centrally regulated by the brain through several interacting neuronal systems. The so-called homeostatic system and the reward and executive control systems are all involved in energy balance (1,4). The homeostatic system, consisting of the hypothalamus and several nuclei in the brainstem, regulates energy intake by combining satiety signals, metabolic and hormonal cues. (5). This is then integrated with signals from the reward system and the executive control system (6). Hedonic processes however can (completely without awareness) override the homeostatic system and lead to obesity via an excessive energy intake relative to metabolic needs (7,8).

A large body of work has shown that in persons with obesity, areas and neuronal networks involved in energy regulation, both in homeostatic and hedonic areas such as the hypothalamus, insula, cingulate and orbitofrontal cortex (OFC), function differently compared with lean subjects (9–17). Generally, in persons with obesity, brain connectivity and activity in these (sub)cortical brain areas and neuronal networks are increased (9,12,13,18). In addition to changes in functional connectivity, structural connectivity is also associated with an elevated body mass index (BMI) (19). Furthermore, responses to fasting and food intake have also been shown to be different

between subjects with and without obesity, predominantly demonstrating an increased activity in brain areas involved in reward systems (9–11,13). Therefore, brain alterations in obesity might be involved in an increased energy intake versus the amount of energy needed for a stable body weight (1).

Although these various changes in brain function have been found in obesity in cross-sectional studies, it remains a question whether and which of these altered brain functions are reversible after significant weight loss (20,21). Weight loss due to bariatric surgery has been shown to decrease the BOLD response to visual food cues (22), indicating that weight loss might influence brain function. However, it remains relatively unclear whether alterations in brain function are cause or consequence of obesity. The aim of the current study was to investigate whether prolonged fasting and/or weight loss influences ('normalizes') neuronal brain activity in participants with obesity and if this correlates with alterations in metabolic markers. To distinguish between differences induced by feelings of hunger or weight loss, effect after prolonged fasting (48 h) and after an 8-week weight loss intervention was examined.

Methods

Study population and design

The current study is based on the population described in Wijngaarden *et al*. (13). In short, participants with obesity were recruited and admitted to the research centre for a 48-h fast, during which several clinical and metabolic measurements were performed. Functional magnetic resonance imaging (fMRI) was performed in the morning after an overnight fast and in the morning after the prolonged 48-h fast in all participants before the start of the weight loss intervention. Measurements were then repeated at a similar time during the morning after an overnight fast in 10 of participants that completed an 8-week weight loss intervention. Fourteen participants with obesity that were otherwise healthy (e.g. non-diabetic) were included at baseline. Inclusion criteria were as follows: Caucasian, healthy, weight stable and with a normal fasting plasma glucose ($\leq$5.6 mmol L^{-1}). Exclusion criteria were: a positive family history of diabetes type 2, smoking, medication use affecting glucose homeostasis and/or brain function. The study was conducted in accordance with the Declaration of Helsinki, informed consent was obtained from all participants and the study was approved by the local institutional review board of the Leiden University Medical Center and registered in the Netherlands Trial Register under number NTR2401. For a more detailed description, methods have also been described by Wijngaarden *et al*. (13).

Weight loss intervention

Participants were prescribed a commercially available very low calorie diet for 8 weeks (Prodimed). This diet is a high-protein low-carbohydrate diet of ±600 kcal d^{-1} consisting of meal replacement products. The study diet completely replaced the normal diet with both liquid a solid meal replacements. The caloric content is very low compared with other weight loss intervention diets and is aimed towards rapid initial weight loss. In addition to the meal replacement products, participants were instructed to drink at least 2 L of water or other sugar-free drinks per day. Additionally, participants were instructed to continue their regular levels of physical activity for the duration of the 8-week intervention. During very low calorie diet, participants were seen and/or phoned on a regular basis to monitor compliance and progress. Additionally, participants visited the research centre every 2 weeks to check for physical or psychological effects. Body weight, blood pressure and heart rate were monitored during these visits.

Magnetic resonance imaging data acquisition

Magnetic resonance imaging scanning was performed on a Philips Achieva 3.0 T scanner using an eight-channel head coil (Philips Healthcare, Best, The Netherlands). For registration purposes, anatomical high-resolution 3D T1-weighted images of the whole brain were acquired (ultra-fast gradient echo acquisition, repetition time [TR] 9.78 ms, echo time [TE] 4.59 ms, flip angle 8, 140 axial slices, Field Of View (FOV) 224 mm × 244 mm, reconstructed in-plane resolution 0.875 mm × 0.875 mm, slice thickness 1.2 mm) along with a high-resolution T2*-weighted echo-planar imaging (EPI) scan (EPI factor 29, 84 axial slices scanned in ascending order, TR 2,200 ms, TE 30 ms, flip angle 80, FOV 220 mm × 220 mm, voxel size 1.96 × 1.96 × 2.0 mm). Resting-state scans were acquired with T2*-weighted gradient EPI (EPI factor 29, 160 volumes, 38 axial slices scanned in ascending order, TR 2,200 ms, TE 30 ms, flip angle 80, FOV 220 mm × 220 mm, isotropic voxel size 2.75 mm with a 0.25-mm slice gap).

Magnetic resonance imaging data preprocessing

Magnetic resonance imaging data were preprocessed and analysed using fMRI of the Brain Software Library (FSL) version 5.0.8 (23). Of all data sets, structural and functional, non-brain structures were removed using

Brain Extraction Tool as implemented in FSL. The T1-weighted images were registered to the 2-mm isotropic MNI-152 standard space image (Montreal Neurological Institute, Montreal, QC, Canada) using non-linear registration with a warp resolution of 10 mm. The fMRI Expert Analysis Tool was used for motion correction with MCFLIRT, spatial smoothing with a full width at half maximum of 3 mm and high-pass temporal filtering with a cut-off frequency of 0.01 Hz. The functional resting-state images were registered to the corresponding T1-weighted images using boundary-based registration affine registration, using the high-resolution echo-planar images as an additional registration step.

Functional connectivity analysis

Magnetic resonance imaging data processing for the functional connectivity analysis was performed as described earlier (24). Functional network analysis was performed on the same ICA-AROMA preprocessed data using the Beckmann resting-state functional networks templates (25). The Beckmann auditory network was used as a template for the salience network as this standard template encompasses largely the same brain areas (26). To account for noise, white matter and cerebral spinal fluid (CSF) templates were included in the analyses. Functional connectivity of each network of interest was calculated using the dual regression approach. This results in 3D images for each individual, with voxel-wise *Z*-scores representing the functional connectivity to each network. The average *Z*-scores per network were calculated for all study time points. Seed analysis of the amygdala and hypothalamus was performed similarly as described previously (13). In the current study, the seed networks were determined for the left and right amygdala and hypothalamus, and *z*-scores per subject were calculated within these seed networks.

BOLD changes analysis

Whole-brain BOLD signal intensities were compared between study visits as performed in previous studies (24) according to Rombouts *et al*. (27) and similar to others (28,29). In short, a single volume BOLD signal map was calculated by averaging the time series data. Average CSF signal of the BOLD image was determined by averaging all voxels within the masked CSF. This CSF mask was determined by selecting voxels located in the lateral ventricles on the segmented structural images. This approach decreases the possibility of including unwanted signal of other compartments than CSF, and one of the main reasons to use CSF as calibration 'tissue' is that differences, or fluctuations, in de-/oxygenation haemoglobin do not affect the CSF signal. Next, in each subject, a normalized BOLD signal map was calculated by dividing each voxel's signal by the average CSF signal. Voxel-wise comparisons of normalized BOLD signal maps between baseline and 48-h fast and baseline and after diet intervention time points were performed using the randomize tool of FSL with a paired samples approach and using threshold-free cluster enhancement (30). After voxel-wise comparisons, mean BOLD signal was calculated for the clusters showing a significant change in BOLD signal compared with baseline. The statistical clusters were binarized and used as masks/region of interest to calculate mean BOLD signal in these clusters per subject for every study time point.

Statistical analysis of quantitative data

Changes in subject characteristics between study time points were analysed by repeated measures analysis of variance. Associations between average BOLD signal in the extracted clusters and metabolic markers were determined using Pearson's correlation coefficient. Associations were determined for glucose, insulin, leptin, weight and BMI. An uncorrected $p < 0.05$ was considered significant.

Results

Subject characteristics at baseline and after diet intervention

Fourteen participants with obesity (two males and 12 females, BMI 35.2 ± 1.2 kg m^{-2}) were included at baseline. Measurements were repeated after a 48-h fast in all participants and after an 8-week diet intervention in 10 of the participants (two exclusions due to dropouts and motion artefacts during scanning, two participants were lost to follow-up due to planning constraints. Participants were unable and/or unwilling to plan their follow-up visits and therefore did not complete all measurements. No loss to follow-up was caused by adverse events or due to medical indications). Subject characteristics for the study group at the different study time points are shown in Table 1. Weight and BMI decreased significantly after the weight loss intervention with a mean weight loss of 12.7 ± 3.5% (range 5.3–18.4%). Leptin and glucose levels decreased significantly compared with baseline after both the 48-h fast and the weight loss intervention. Insulin levels were significantly decreased after the 48-h fast but were not significantly lowered after the weight loss intervention.

Table 1 Subject characteristics

	Baseline (n = 14)	After 48-h fast (n = 14)	After diet (n = 10)
Age (years)	30 ± 3		
Height (m)	1.74 ± 0.08		
Sex (female/male)	12/2	12/2	8/2
Weight (kg)	107 ± 16	104 ± 4*	95 ± 4*
BMI (kg m^{-2})	35.2 ± 4.3	34.4 ± 1.2*	31.5 ± 1.3*
Fasted insulin (mU L^{-1})	19.6 ± 7.9	3.2 ± 3.0*	19.9 ± 8.6
Fasted glucose (mmol L^{-1})	5.0 ± 0.7	4.0 ± 0.6*	4.6 ± 0.7*
Fasted leptin (μg L^{-1})	36.2 ± 13.3	20.6 ± 11.8*	13.7 ± 8*

Values in mean ± standard deviation. BMI, body mass index.
*Significantly different from baseline at $p < 0.05$ (repeated measures analysis of variance).

Functional connectivity changes

Figure 1 shows the z-scores for functional connectivity of the salience, sensory motor, default mode and executive control networks and the left/right amygdala and hypothalamus seeds at all three study occasions. No significant changes in Z-scores were found between the different study occasion in any of the networks or of any of the seeds.

Qualitative and quantitative BOLD signal changes

The 48-h fast intervention did not lead to significant voxel-wise changes in BOLD signal. The dietary weight loss intervention resulted in a significant voxel-wise decrease in BOLD signal in parts of the insula, OFC and in areas of several frontal gyri (Figure 2). The quantitative BOLD signal was determined in the clusters showing significant changes after weight loss. The mean quantitative BOLD signals for all three measured time points are shown in Figure 3 for the three main clusters containing the OFC, the insula and middle and inferior frontal gyri. The mean BOLD signals in the OFC cluster and the insula clusters were significantly decreased after the diet intervention ($p < 0.0001$) but not show changes in signal after the 48-h fast ($p = 0.252$ and $p = 0.687$, respectively). The mean BOLD signal in the middle and frontal gyri cluster was significantly decreased after weight loss ($p < 0.0001$) but also showed a significant decrease in BOLD signal after the 48-h fast ($p = 0.043$).

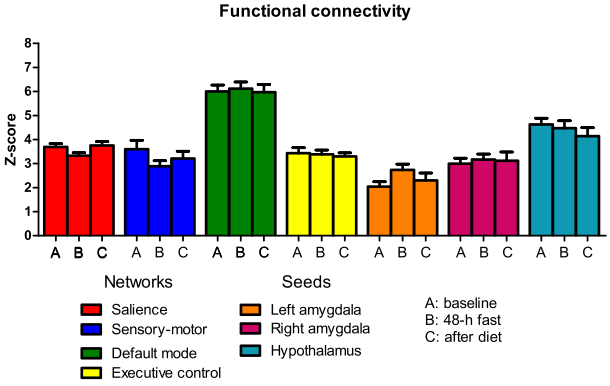

Figure 1 Functional connectivity changes after diet intervention. Functional connectivity reported as Z-scores in functional networks and of amygdala and hypothalamus seeds per study time point. Data depicted as mean with standard error.

Correlation between BOLD activity and metabolic markers

Scatter plots for the correlation at baseline between leptin and BMI with the BOLD signals in the clusters are shown in Figure 4.

Leptin

At all the three different time points (overnight fast, 48-h fast and after weight loss intervention), leptin showed a significant positive correlation with the activity in the OFC, insula and frontal gyri. At baseline (overnight fast), the correlation coefficient for the BOLD signal in the OFC was 0.625 ($p = 0.017$); for the insula, it was 0.590 ($p = 0.026$); and for the frontal gyri, it was 0.745 ($p = 0.002$). After the diet intervention, the correlations were similar or stronger. The correlation coefficient for the BOLD signal in the OFC was 0.639 ($p = 0.047$); for the insula, it was 0.768 ($p = 0.009$); and for the frontal gyri, it was 0.742 ($p = 0.014$).

Body mass index

Body mass index showed a significant positive correlation with the activity in the OFC and frontal gyri, but not the insula, at several but not all of the measured study time points. At baseline, the correlation coefficient for the BOLD signal in the OFC was 0.433 ($p = 0.122$), and for the frontal gyri, it was 0.683 ($p = 0.007$). After the diet intervention, the correlation coefficient for the BOLD signal in the OFC was 0.684 ($p = 0.029$), and for the frontal gyri, it was 0.696 ($p = 0.026$).

Insulin/glucose

At baseline, no association was found between insulin and glucose with the BOLD signal. After the 48-h fast only, insulin levels showed a positive correlation with the activity in all three clusters.

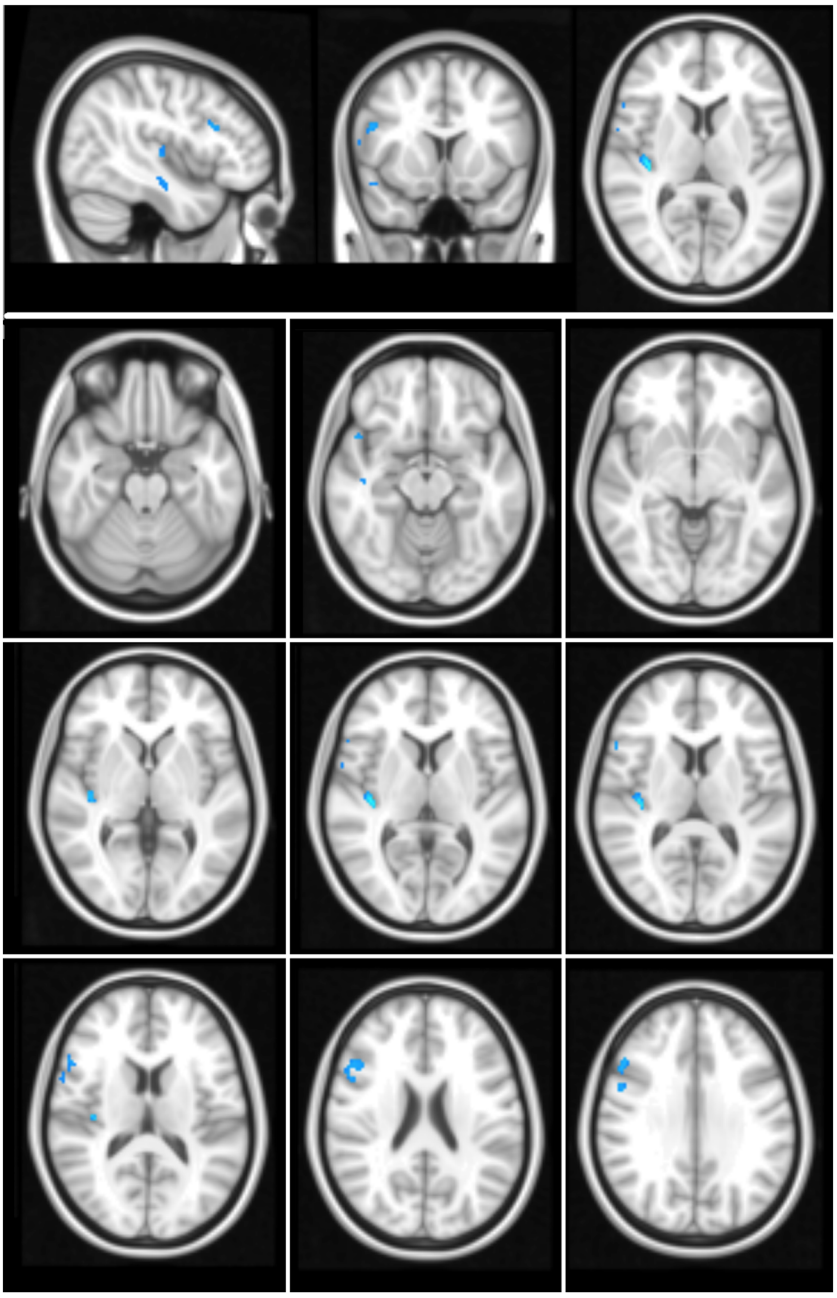

Figure 2 Brain areas with significant changes in BOLD signal/neuronal activity after diet intervention. Decreases in BOLD signal between the baseline and after diet intervention are shown in blue scale (Family-Wise Error (FWE) corrected).

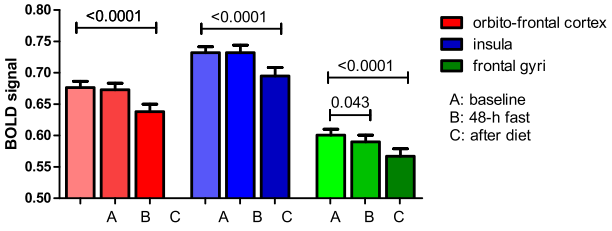

Figure 3 Quantitative BOLD signal in significantly affected clusters per study time point. Data depicted as mean with standard error.

The change in leptin, glucose, insulin and BMI after weight loss did not show a correlation with the change in BOLD signal in the affected clusters.

Discussion

The results of this study show that an 8-week weight loss intervention, but not a 48-h fast, significantly decreased BOLD signal in parts of the insula, OFC and in areas of

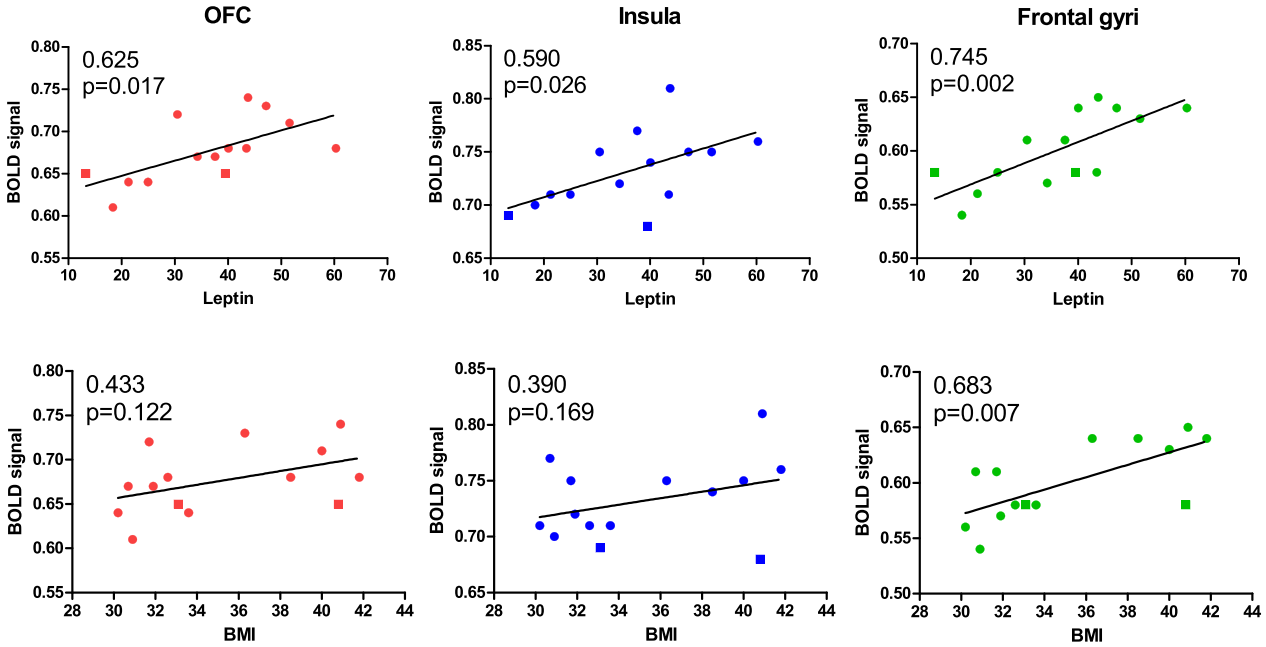

Figure 4 Scatter plots indicating the correlation between leptin and body mass index (BMI) and BOLD signal in the significantly affected clusters. Leptin in $\mu g\ L^{-1}$, BMI in $kg\ m^{-2}$, female participants indicated as circles and male participants indicated as squares. Uncorrected *p*-values are reported. OFC, orbitofrontal cortex.

several frontal gyri, indicating a decrease in neural activity in these brain areas. Additionally, the neuronal activity in these areas was correlated with leptin and BMI. The weight loss intervention did not have any effects on functional network connectivity of the default mode, salience and executive control networks or connectivity of the amygdala and the hypothalamus with the rest of the brain.

The areas of the brain that showed decreased neuronal activity after weight loss are brain areas that have previously been shown to function differently in obesity (9–17). Most of these studies show that the activity and/or connectivity in these areas is increased in obesity compared with lean subjects. Although no direct comparison of the results to lean participants was possible, it might be that the decreases in activity found after weight loss in these areas are an indication of normalization of brain activity in these areas. However, one could also speculate that these alterations after weight loss might even drive food intake leading to regaining of weight after the diet has ended. Interestingly, the current findings are in line with a recent study showing alterations in the same brain areas (insula and frontal cortex) upon a weight loss intervention (31). This study did look at changes in functional connectivity instead of BOLD activity, which is a different measure of brain function, but the areas affected by the weight loss intervention are nonetheless very similar.

No voxel-wise changes in BOLD signal after the 48-h fast were found in the current study. This suggests that the decreases in neuronal activity might not be caused by short-term metabolic changes or changes in feelings of hunger and satiety caused by fasting but are more likely related to actual decreases in body weight. No effects of 48-h fast and weight loss intervention were found on functional connectivity of several functional networks and region of interest involved in feeding behaviour. However, in an earlier study, several differences in changes in functional connectivity were found between the hypothalamus and the insula and anterior cingulate cortex after an 48-h fast in participants with obesity versus the changes found in healthy controls using a seed-based approach (13), indicating that participants with obesity might respond differently to fasting than lean participants, but the effects of fasting within the patient group are not as strong.

In the current study, although no connectivity changes and whole-brain effects of the 48-h fast were found when looking at the mean BOLD signal in the affected clusters, a significant decrease in the frontal gyri cluster after the 48-h fast was found. A possible explanation for the results in the current and previous study is that the effects of fasting lead to more subtle changes in brain function, which can be detected with more specific region to region analysis but do not lead to more global effects on brain function. Furthermore, the spatial resolution of the current whole-brain approach might not be high enough to detect changes in small brain areas such as the hypothalamus.

The brain areas showing decreases in activity after weight loss are known to be involved in regulation of energy balance and feeding behaviour (4). As mentioned, both the homeostatic control and hedonic and executive control systems work in concert to regulate energy balance (1,4). The areas showing a decrease in activity after weight loss are mainly involved in the hedonic and executive control systems and less in the homeostatic system. The insula is involved in determining salience of incoming stimuli (32) and in taste perception (33). Due to the combination of these functions, the insula is therefore involved in palatable feeding. The insula has been shown to have a stronger BOLD response to ingestion of sucrose in adolescents with obesity compared with lean subjects (34). And the insula has different functional connectivity patterns in patients with obesity versus normal weight subjects (17).

Similar to the insula, the OFC is also involved in determining salience due to its role in the limbic system and executive functioning (35,36). The OFC is important in determining reward and affective value of food via stimuli including taste (37). Furthermore, the OFC has been indicated as an important structure in termination of food intake, and this function has been shown to be disrupted in obesity (16).

The decreases in neuronal activity in both the insula and OFC found in the current study could indicate a change in reward and salience response after weight loss. Furthermore, the areas responding to weight loss showed overlap with brain areas that responded to glucose ingestion in an earlier study (24). In this study, decreases in activity were found in the insula, thalamus, anterior cingulate gyrus, OFC, amygdala, hippocampus and the occipital cortex in response to glucose; these areas are involved in hunger and satiety, indicating a satiety response after energy ingestion. This indicates that the decrease neuronal activity in these brain areas might lead to a different satiety response after weight loss.

A main limitation of the current study is the study population. The sample size of the current study is limited and consists mostly of female participants due to a low response to advertisement, especially by male participants. Because it is known that there are several sex-specific differences in energy metabolism (38), it can be expected that sex differences in the brain responses measured in this study are present. Due to limited sample size, analyses were not controlled or corrected for the menstrual cycle and/or oral contraceptive use in the female participants. Furthermore, it would be an interesting – but probably unethical – experiment to compare the effects of weight loss in participants with obesity to the effects of weight loss in lean subjects to determine if the effects are caused by loss of excess weight or weight loss in general. Additionally, it would be interesting to follow up participants after weight loss to determine if the effects on the brain activity are maintained when participants return to a less restrictive diet.

In addition to the significant changes in neuronal activity after weight loss, the neuronal activity in the responsive areas was correlated with hormonal and metabolic markers of obesity. Central regulation of energy balance is known to be influenced by peripheral hormonal signal, both in response to energy intake and in response to long-term signals of energy balance such as leptin (5,39). Earlier research has shown that various functional brain responses are affected by hormonal signals such as insulin and leptin (40,41) and that changes in BOLD responses to visual food cues correlate with changes in ghrelin (22). A positive correlation between leptin and BMI and the BOLD signal in the affected brain areas was found, indicating that high BMI and high leptin levels are associated with a high activity in these brain areas. The change in leptin, glucose, insulin and BMI after weight loss did not show a correlation with the change in BOLD signal in the affected clusters, perhaps due to the small sample size and therefore limited statistical power. However, weight loss did lead to significant decreases in BMI and leptin levels and to decreases in neuronal activity in the current study. This further substantiates that the activity in these brain areas might be related to body weight instead of feelings of hunger, as leptin, insulin and BMI are all correlated with fat mass and body weight.

Taken together, when studying brain function before and after a weight loss intervention, no significant changes in functional connectivity were found, but a decreased activity in brain areas important for feeding behaviour and reward processing was found. Furthermore, the neuronal activity in these brain areas was correlated with metabolic markers of obesity. These results might indicate that alterations in neural activity are reversible, although no comparison with lean individuals was performed in this study. Besides, because it is well known that many patients with obesity cannot maintain weight loss for a longer period of time, the exact connotations of these findings still need to be established.

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after publication. Additionally, an abbreviated version of the study protocol is available at www.trialregister.nl under number NTR2401.

Trail Registration

The study is registered in the Netherlands Trial Register (NTR) under number NTR2401 at www.trialregister.nl.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

Author Contributions

H. P., J. v. d. G. and M. W. designed the research; M. W. and J. v. d. G. conducted the research; A. M. v. O. analysed the data; A. M. v. O., M. W., J. v. d. G. and H. P. wrote the paper; and J. v. d. G. had primary responsibility for the final content. All authors read and approved the final manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. CONSORT participant diagram