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Versteeg, R.I.

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Meal timing during weight loss differentially affects brain responses to visual food cues in the caudate nucleus of obese men.
Abstract

Background
Weight loss increases the reward value of food which is associated with a lower success rate of weight loss maintenance. Meal timing during caloric restriction is a determinant of weight loss and post-diet weight maintenance but the underlying mechanism is unknown. We hypothesized that during a hypocaloric diet, eating most of the calories in the morning compared to the evening reduces the anticipatory reward response to food, assessed as brain activity responses to visual food cues.

Method
We studied the effects of eating 50% of daily calories in the morning (BF-group) or in the evening (D-group) during a 4-weeks hypocaloric diet on brain oxygen level dependent (BOLD) responses to visual food cues in 23 obese men.

Results
Weight loss did not differ between the BF- and D-group (-6.5%±1.5 vs -6.2%±1.9 respectively). BOLD signal in response to high calorie food pictures was significantly increased in the putamen and pallidum in both diet groups after weight loss. Interestingly, in the caudate nucleus, the BF-group showed decreased neuronal activation, whereas the D-group showed increased neuronal activation upon high calorie visual food cues, resulting in a significant change over time between both diet groups.

Conclusion
During caloric restriction and weight loss, meal timing differentially affects BOLD responses to high calorie visual food cues in the caudate nucleus. With similar weight loss, obese men that consumed most calories in the morning showed a reduced neuronal response in the caudate nucleus while the dinner group had an increased response. A lower visual food cue-mediated activity response in a brain area involved in the motivation to eat might mediate the positive effect of meal timing on body weight loss maintenance.
Introduction

Using functional magnetic resonance imaging (fMRI), obese subjects show increased brain activity in reward areas, including in the insula, orbital frontal cortex (OFC), caudate nucleus, putamen, ventral tegmental area (VTA) and nucleus accumbens (NAc) (1, 2) in response to high calorie food pictures, and this response is predictive of weight gain over the next year (3). This suggests a direct link between brain activation in reward areas and body weight regulation. During fasting conditions, brain oxygen level dependent (BOLD) responses to high calorie visual food cues in reward areas are higher compared to the satiated condition (4-6), suggesting that food is more rewarding in a state of negative energy balance. In line, a longer-term negative energy balance and weight loss increase BOLD signal in the caudate nucleus in healthy subjects compared to those in a neutral or positive energy balance (7). However, fMRI-studies report mixed effects of weight loss on neuronal responses to food cues in obese subjects with some studies showing increased activation (8-10) and others report decreased activation in reward areas (11, 12). Interestingly, obese subjects who are least successful in losing weight during a hypocaloric diet intervention, show increased pre-diet activation of reward areas in response to high calorie food pictures. In addition, weight loss maintenance during the follow-up period is predicted by these visual food cues-mediated responses measured after the diet intervention period (12). Finally, short-term overfeeding in lean individuals leads to a reduction in BOLD activation to food cues in reward related areas (13). Collectively, these studies show the importance of external visual food cues in the regulation of energy balance. During caloric deprivation, increased activation of reward circuits in response to food cues may promote the intake of calorie dense food and could explain the low rate of long-term success of hypocaloric diets.

Recent studies suggest that besides total caloric intake, the timing of consuming calories across the day modulates body weight and overall food intake. Several cross-sectional studies show that eating most of the calories in the morning compared to the evening is associated with less overall caloric intake and lower body mass index (BMI), especially during caloric restriction (14, 15). Furthermore, obese subjects who consume most of the calories in the morning during a hypocaloric diet showed more weight loss (16) and were more successful in maintaining reduced body weight (17). From these studies, it seems that the caloric distribution across the day plays a role in long-term weight loss, although the underlying mechanism is unclear.

Since long-term weight loss is accompanied by changes in reward areas favoring food intake and meal timing affects food intake and body weight with positive effects of eating most of the daily calories in the morning, we hypothesized that during caloric restriction, consuming 50% of total calories in the morning compared to the evening reduces brain activity responses to high calorie food cues.
Methods

Participants
We included 25 obese men (BMI ≥ 30kg/m², age 50-80 years) with a stable weight three months prior to inclusion. They all had impaired fasting glucose defined as fasting plasma glucose levels ≥ 5.6 mmol/l (18) and/or were insulin resistant defined as fasting insulin levels ≥ 73 pmol/l (19). Exclusion criteria were use of any medication except for anticoagulants, 5-alpha reductase inhibitors and those related to treatment of components of the metabolic syndrome (excluding insulin, oral glucose lowering drugs and beta-blockers), history of any psychiatric disorder, shift work, irregular sleep pattern, regular vigorous exercise, restrained eaters, history of eating disorder, alcohol/drug abuse and smoking. Subjects were recruited via local advertisements. The trial was performed between November 2014 and January 2016 and registered at the national trial register as NTR-5399. All subjects provided written informed consent. The study was approved by the medical ethics committee of the Academic Medical Centre, Amsterdam and conducted according to the Declaration of Helsinki of October 2013.

Study design and dietary intervention
We performed a randomized controlled intervention study. At inclusion, the Munich ChronoType Questionnaire (MCTQ) and Eating Disorder Examination-Questionnaire (EDE-Q) were used to determine subjects’ chronotype and to assess restrained eating behavior respectively (20). After inclusion, subjects consumed an eucaloric weight maintaining diet during a one-week run-in phase. The eucaloric diet was based on measured resting energy expenditure (REE) using indirect calorimetry (Vmax Encore 29, Carefusion, San Diego, CA, USA) at the beginning and end of the run-in week. Subsequently, participants were randomized into one of two hypocaloric diet groups for 4 weeks (50% of caloric need calculated as 1.3 x REE x 0.5). The breakfast (BF) group consumed 50% of the daily calories at breakfast, 35% at lunch and 15% at dinner. The dinner (D) group consumed 15% of the daily calories at breakfast, 35% at lunch and 50% at dinner. Subjects replaced their breakfast and dinner by a protein enriched liquid meal (Fresubin protein energy drink; Fresenius Kabi, Bad Homburg, Germany) with a nutritive value of 1.5 kcal/ml; 27 energy% protein, 32.3 energy% carbohydrates, and 40 energy% fat (9% saturated fatty acids, 73% monounsaturated fatty acids, 18% polyunsaturated fatty acids) and by one bar (Modifast ProtiPlus; Nutrition & Santé Benelux, Breda, the Netherlands) with a nutritive value of 94 kcal; 36 energy% protein, 36 energy% carbohydrates, and 28 energy% fat (36% saturated fatty acids). The amount of liquid drink per serving was calculated based on daily caloric need. For lunch, subjects chose between different menus, consisting of sandwiches with savory fillings. The amount of kcal and macronutrient compositions did not differ between lunch menus. Subjects were instructed to take their breakfast between 7 and 9 AM, lunch between 12 AM and 14 PM and dinner between 18 and 20 PM. Subjects visited the research unit every week to monitor dietary intake, body weight and to assess REE. They reported dietary intake and meal timing on a special designed diary to increase compliance (www.mijnvoedingscentrum.nl/eetmeter).
fMRI paradigm
Before and after the diet, subjects underwent two separate fMRI imaging sessions 90 minutes after eating a small snack with a nutritive value of 94 kcal (Modifast ProtiPlus; Nutrition & Santé Benelux, Breda, the Netherlands) in the afternoon. Visual stimuli consisted of 126 high-quality color pictures selected from a previous study (21). Pictures were subdivided into 3 categories: 1) high calorie food (HC), 2) low calorie (LC) food and 3) non-food (NF). High calorie food pictures consisted of sweet and savory foods including ice cream, chocolate chip cookies, cheesecake, French fries, hamburgers and pizza. Low calorie food pictures consisted of fruit and vegetables including fruit salads, apples, strawberries, garden salads, cucumber and tomatoes. Non-food pictures consisted of rocks, shrubs, bricks, trees and flowers. All pictures were presented via Eprime 1.2 (Psychology Software Tools, Inc., Pittsburg, PA) in a block design format, with a total of 3 runs. Each run consisted of 6 blocks of pictures: 2 blocks of HC, 2 blocks of LC and 2 blocks of NF pictures. Within each block of 21 seconds, 7 individual pictures were presented for 2.5 seconds each followed by a 0.5 second gap. The blocks were separated by 9 seconds of grey blank screen with a fixation cross. The order of blocks was randomized from run to run with the constraint that a given picture category was not followed by the same category. Pictures were matched across blocks and sessions for shape and color. Because each participant was scanned 2 times, 2 versions with different pictures but identical design were created. The sequences of blocks were randomized across both visits. Pictures were projected onto a screen behind the participant and viewed via a 45° mirror attached to the head coil. An overview is presented in figure 1.

Figure 1. fMRI paradigm. One of the three runs within one fMRI session. Each run consisted of 6 blocks of pictures of high calorie foods, low calorie foods and non-food pictures. Each block contained seven pictures.

fMRI data acquisition
MRI data were acquired on a 3.0T Philips Ingenia scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel receive-only head coil. A 3D anatomical MRI was obtained using a T1-weighted sequence. fMRI data were acquired using an echo planar imaging T2* weighted Blood Oxygen Level Dependent (BOLD) sequence with the following scan parameters: Repetition time = 2000 ms, Echo Time = 27 ms, 3 mm isotropic resolution field of view = 240 x 240 x 122, 0.3 mm gap, flip angle = 80°) with 37 ascending slices per volume (3 mm thickness, 0.3 mm gap).
**fMRI data analysis**

Image analysis was performed with SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK) in MATLAB (version R2013a, Mathworks, Inc., Sherborn, MA). Functional images were slice-time corrected, realigned to the first volume to correct for head motion, co-registered to the individual's anatomical MRI, normalized to Montreal Neurological Institute (MNI) space and spatially smoothed using an 8 mm full width at half maximum Gaussian kernel. The first level analysis included the three experimental conditions (HC, LC, NF) modeled as a boxcar convolved with a canonical hemodynamic response function. A high-pass filter (cut-off 1/128 Hz) was included in the first level model to remove low-frequency noise. For each subject and each time point contrast images were computed for the following comparisons: 1) HC vs NF 2) HC vs LC 3) LC vs NF 4) all food (HC + LC) vs NF. Contrasts were entered into second-level analyses in order to determine the main effect of task (family-wise error (FWE) rate corrected for multiple comparisons at a cluster level threshold of p<0.05). We examined the interaction between conditions (before vs after diet) and groups (BF vs D) using whole-brain and ROI analysis for all contrasts. A priori defined ROI’s were bilateral caudate nucleus (including separate ROI for the head, body and tail), putamen and pallidum, defined using masks provided by the Anatomical Automatic Labeling (AAL) in the WFU Pickatlas toolbox (22). Beta-values from the contrast maps were extracted using MarsBar (MRHC Cognition and Brain Sciences Unit, Cambridge, UK). Subsequently, beta-values were entered into SPSS to assess statistical significance (p<0.05 was considered significant).

**Laboratory analysis**

Plasma glucose levels were determined immediately using the glucose oxidation method with the Biosen glucose analyzer (EKF Diagnostics, Barleben, Germany). Insulin levels were determined by immunoassay on an IMMULITE 2000 system (Diagnostic Products, Los Angeles, CA).

**Statistics**

Normally distributed variables are presented as mean ± standard deviation. Baseline characteristics between the BF- and D-group were compared by a two-sided independent-samples Student’s T-test. Within subject changes before and after the diet were analyzed using a two-sided paired samples Student’s T-test. Differences between the BF- and D-group over time (between group differences) were tested using two-sided independent samples Student’s T-test. All data were analyzed using SPSS for Windows, version 23 (SPSS Inc. Chicago, Illinois, USA).
Results

Baseline characteristics
Subjects participated in a study on the effect of meal timing and weight loss on 1. glucose metabolism (chapter 6), 2. changes in brain dopamine and serotonin systems (chapter 4) and 3. changes in brain activity responses to food cues in reward areas. Forty-five subjects were screened, of which 25 subjects were included. After the run-in week, two subjects dropped out due to 1) claustrophobia during the MRI and 2) work schedule that interfered with the study protocol. Twenty-three obese men completed the diet. Twelve men were randomized to the BF-group and 11 men to the D-group. Baseline characteristics were similar between both diet groups and are presented in Table 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BF-group</th>
<th>D-group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60.7 ± 7.7</td>
<td>59.0 ± 8.5</td>
<td>0.63</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>108 ± 13.0</td>
<td>111 ± 16.6</td>
<td>0.64</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>34.2 ± 4.2</td>
<td>34.3 ± 3.7</td>
<td>0.95</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.5 ± 0.8</td>
<td>5.3 ± 0.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>121 ± 72.4</td>
<td>110 ± 35.6</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

Dietary intake and weight loss
Total daily caloric intake and macronutrient composition did not differ between the BF- and D-group (1257 ± 134 vs 1298 ± 140 kcal, p=0.48 respectively). In addition, the time at which breakfast (8:20 ± 0:36 vs 8:27 ± 0:23 h, p=0.57), lunch (13:08 ± 0:35 vs 12:58 ± 0:16 h, p=0.41), and dinner (18:44 ± 0:44 vs 18:33 ± 0:22 h, p=0.29) was consumed did not differ between both diet groups. Body weight was significantly decreased in all subjects after the diet (110 ± 14.6 kg before diet vs 103 ± 14.5 kg after diet, p=<0.001). Both, subjects in the BF- and D-group reduced absolute and percentage weight loss equally (7.0 ± 1.4 vs 6.8 ± 2.0 kg, p=0.86 and 6.5 ± 1.5 vs 6.2 ± 1.9 %, p=0.70 respectively).

Baseline brain responses to visual food cues
fMRI data of one subject in the BF-group and one subject in the D-group were missing due to technical issues with the MRI scanner. Clusters of significant activation in response to HC vs NF, HC vs LC, LC vs NF and all food vs NF for all subjects are presented in Table 2 and Figure 2. The largest cluster of cue-related effects across conditions was observed in the occipital region, followed by several regions in the temporal and parietal lobe.
Figure 2. Baseline activation (BOLD) in response to high calorie vs non-food (MNI coordinates 4, -16, 8). The color scale reflects the T value of the functional activity. Results are presented as threshold P<0.001, FEW corrected on the basis of cluster extend.

Table 2. Baseline main effects of task for all subjects

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Region</th>
<th>Side</th>
<th>Cluster</th>
<th>p-FEW</th>
<th>MNI (x,y,z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High calorie &gt; non-food</td>
<td>Occipital inferior</td>
<td>L</td>
<td>778</td>
<td>&lt;0.001</td>
<td>-48 -73 -5</td>
</tr>
<tr>
<td></td>
<td>Temporal middle</td>
<td>R</td>
<td>896</td>
<td>&lt;0.001</td>
<td>48 -61 -2</td>
</tr>
<tr>
<td></td>
<td>Precentral</td>
<td>L</td>
<td>201</td>
<td>0.002</td>
<td>-48 2 31</td>
</tr>
<tr>
<td></td>
<td>Parietal inferior</td>
<td>R</td>
<td>161</td>
<td>0.005</td>
<td>30 -55 49</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus</td>
<td></td>
<td>491</td>
<td>&lt;0.001</td>
<td>-6 35 58</td>
</tr>
<tr>
<td></td>
<td>Precentral</td>
<td>R</td>
<td>237</td>
<td>0.001</td>
<td>57 2 31</td>
</tr>
<tr>
<td></td>
<td>Parietal superior</td>
<td>L</td>
<td>150</td>
<td>0.007</td>
<td>-30 -55 58</td>
</tr>
<tr>
<td></td>
<td>Superior motor area</td>
<td></td>
<td>108</td>
<td>0.026</td>
<td>0 2 64</td>
</tr>
<tr>
<td>High calorie &gt; low calorie</td>
<td>NA</td>
<td></td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Low calorie &gt; non-food</td>
<td>Occipital middle</td>
<td>L</td>
<td>962</td>
<td>&lt;0.001</td>
<td>-42 -85 4</td>
</tr>
<tr>
<td></td>
<td>Parietal superior</td>
<td>R</td>
<td>192</td>
<td>0.002</td>
<td>33 -49 55</td>
</tr>
<tr>
<td></td>
<td>Temporal inferior</td>
<td>R</td>
<td>971</td>
<td>&lt;0.001</td>
<td>51 -61 -5</td>
</tr>
<tr>
<td></td>
<td>Precentral</td>
<td>L</td>
<td>245</td>
<td>0.001</td>
<td>-48 2 31</td>
</tr>
<tr>
<td></td>
<td>Parietal superior</td>
<td>L</td>
<td>103</td>
<td>0.029</td>
<td>-33 -7 26</td>
</tr>
<tr>
<td></td>
<td>Frontal superior medial</td>
<td></td>
<td>238</td>
<td>0.001</td>
<td>-9 50 40</td>
</tr>
<tr>
<td></td>
<td>Cingulum middle</td>
<td>L</td>
<td>181</td>
<td>0.003</td>
<td>0 26 31</td>
</tr>
<tr>
<td>All food &gt; non-food</td>
<td>Occipital inferior</td>
<td>L</td>
<td>840</td>
<td>&lt;0.001</td>
<td>-48 -73 -8</td>
</tr>
<tr>
<td></td>
<td>Temporal inferior</td>
<td>R</td>
<td>518</td>
<td>&lt;0.001</td>
<td>48 -70 -11</td>
</tr>
<tr>
<td></td>
<td>Hippocampus</td>
<td>L</td>
<td>209</td>
<td>0.003</td>
<td>-30 -4 26</td>
</tr>
<tr>
<td></td>
<td>Precentral</td>
<td>L</td>
<td>128</td>
<td>0.015</td>
<td>-45 2 34</td>
</tr>
</tbody>
</table>

p-TEW = p-value Family-Wise Error correction for multiple comparison across whole brain; R = right; L = left; MNI = Montreal Neurological Institute coordinates in mm, NA = Not applicable
Main effect of weight loss

Whole brain analyses did not reveal significant differences over time for any of the contrasts, whereas ROI analysis showed significant increased brain activation in the putamen and pallidum in response to HC vs NF (p=0.038 and p=0.011 respectively) and to HC vs LC (p=0.002 and p=0.008 respectively) after the diet (Figure 3). No effects were observed in the caudate nucleus and changes over times were not significant for other contrasts.

![Brain ROIs](image)

Figure 3. Neuronal activation was significantly increased in response to high calorie vs non-food pictures (A) and high calorie vs low calorie pictures (B) in the putamen and pallidum after the diet. Data are expressed as mean ± SEM.

Meal timing effects

Whole brain analyses showed no interaction effect between condition (before vs after diet) and group (BF vs D) for any of the contrasts. ROI analyses of the caudate nucleus showed a decrease in mean activation in the BF-group, whereas in the D-group mean activation increased in response to HC vs NF, resulting in a significant difference over time between both diet groups (Figure 4A; p=0.043). We identified no interaction effects for other contrasts (HC vs LC, LC vs NF and all food (HC + LC) vs NF) in the caudate nucleus neither for any of the contrasts in the putamen and pallidum. In addition, we performed an exploratory voxel-wise analysis to determine differences over time within the caudate nucleus and found a decrease in activation in the head of the caudate nucleus in the BF-group and an increase in the D-group in response to HC vs NF, resulting in a significant difference over time between both diet groups (p=0.006) (Figure 4B). There were no interaction effects in the body and tail of the caudate nucleus.
Figure 4. Meal timing differentially affected brain responses to high calorie vs non-food pictures in the caudate nucleus between the BF- and D-group (A); exploratory analysis show a predominant effect in the head of the caudate nucleus (B).

Discussion

We show, using fMRI, that caloric restriction and weight loss induce an increase in brain activity responses to high calorie food cues in the putamen and pallidum in obese men. We further demonstrate that meal timing differentially affects neuronal activation patterns in the caudate nucleus. Subjects who consumed 50% of their daily calories in the morning showed reduced BOLD responses, whereas subjects who consumed most of their calories in the evening showed increased BOLD responses to high calorie food cues in the caudate nucleus. An additional exploratory analysis revealed that the decrease in BOLD signal in the BF-group was predominantly in the head of the caudate nucleus. These differences between the BF- and D-group were independent of weight loss and dietary intake.

It has been suggested that increased activation in reward areas upon visual food cues might be linked to an increase in anticipation of food consumption (23). Moreover, an earlier fMRI study reported that higher brain activation in response to food pictures in reward circuits after a hypocaloric diet intervention was associated with a lower rate of successful weight maintenance during the follow-up period (12). Thus, the increased BOLD signal we found in our subjects after weight loss in putamen and pallidum, both important for the regulation of food...
intake (24-26), suggests that diet-induced weight loss increases the reward value of food probably aimed at enhancing the motivation to obtain calorie dense food during times of energy restriction. This physiological adaptation might account for the high failure rate of dietary interventions in obesity. Earlier contradictory results on effects of weight loss on BOLD signal in reward areas (8, 9, 11, 12, 27) may be explained by heterogeneity of study variables across studies such as included participants, fMRI parameters (block design vs event-related), duration of the diet intervention, amount of weight loss and fasting or non-fasting state. Fasting duration is an important determinant of food reward responsiveness as caloric deprivation increases neuronal responses to food cues (28), possibly as a result of increased desire for food when people are hungry (29). Moreover, also the conditions of weight loss affect brain responses as subjects that lose weight on a hypocaloric diet showed activations in other brain regions than people with bariatric surgery-induced weight loss (10).

Besides a general effect of weight loss and caloric restriction on visual food cue induced brain activation in putamen and pallidum, we here show a differential effect of meal timing during caloric restriction on BOLD responses in the caudate nucleus in obese men. Our findings might explain the earlier observation on the beneficial effects of consuming more calories in the morning than in the evening on weight loss during and after a dietary intervention (16, 17). The caudate nucleus is involved in the liking and craving components of food intake and less activation in this region, in response to high calorie food pictures upon weight loss, could render obese individuals less sensitive to overeating calorie dense food after weight loss (30). In line, increased neuronal activation in response to visual food cues in the striatum after diet-induced weight loss was negatively associated with weight loss maintenance during a follow-up period (12), while increased activation in the caudate nucleus in response to consuming a milkshake is associated with less weight (re)gain (31).

Interestingly, we show in an exploratory ROI analysis that the differences in brain responses between the BF- and D-group were mainly in the head of the caudate nucleus, which is part of the ventral striatum (32). The ventral and dorsal striatum are functionally different in regulation of food intake. The dorsal striatum is essential for eating habits and cognition whereas the ventral striatum has been implicated in the liking properties of food intake (33, 34). Less is known, however, about the exact role of the ventral caudate nucleus in relation to food intake as studies about the function of the ventral striatum often include the NAc. The ventral striatum receives neural innervation from cortical, insular and midbrain structures and plays an important role in determining goal-directed feeding behavior. Future studies are needed to show whether these changes in brain activity in response to visual food cues result in altered responses in the caudate nucleus when consuming palatable food and whether this influences subsequent longer-term food consumption and body weight.

Our study has some limitations. We included older men and it is unclear whether we can extrapolate these findings to women and men of other age groups. Secondly, we have no longer-term follow-up data to study whether our imaging findings are related to weight maintenance or weight regain.
In conclusion, we show that caloric restriction and weight loss in obese men increase brain activity responses to high calorie visual food cues in putamen and pallidum. Furthermore, consuming most of the daily calories in the morning compared to in the evening has a differential effect on brain activity responses to visual food cues in the caudate nucleus with a lower response in the ventral caudate nucleus in the BF-group and an increased response in the D- group. The increased response might trigger intake of high calorie food with subsequent weight regain after weight loss while the lower response might explain the favorable effects of eating most calories in the morning on body weight regulation during and after caloric restriction in obesity. Our data provide novel insight into meal timing effects on weight loss and weight maintenance.
References


