Daytime sleepiness affects prefrontal regulation of food intake☆


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A B S T R A C T

The recent epidemic of obesity corresponds closely with the decline in the average number of hours of sleep obtained nightly. While growing research suggests that sleep loss may affect hormonal and other physiological systems related to food intake, no studies have yet explored the role that sleepiness may play in reducing prefrontal inhibitory control over food intake. Because evidence suggests that women may be more prone to obesity and eating disorders, as well as more likely to suffer from sleep problems, we examined the relation between general daytime sleepiness, brain responses to food stimuli, and self-reported overeating separately for men and women. Thirty-eight healthy adults (16 women; 22 men) aged 18 to 45 underwent functional magnetic resonance imaging (fMRI) while viewing pictures of high- and low-calorie foods. Subjects completed the Epworth Sleepiness Scale (ESS) and provided a rating to the query “how often do you eat more than you intend to.” Contrast images comparing brain activation derived from the high-versus low-calorie conditions were correlated voxel-wise with scores from the ESS in a second-level regression model, the output of which was used to predict self-reported overeating. As hypothesized, daytime sleepiness correlated with reduced activation in the ventromedial prefrontal cortex during perception of high-versus low-calorie food images. Moreover, activation within this cluster predicted overeating, but only for women. Findings suggest that normal fluctuations in sleepiness may be sufficient to affect brain regions important for regulating food intake, but that these effects may differ between men and women.

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Introduction

Over the past several decades there has been an alarming increase in the rate of excessive weight gain in Western societies (Flegal et al., 2002), with over one in three adults in the United States now meeting criteria for obesity (Ogden et al., 2012). While there are many factors that have arguably contributed to this trend, it is hard to ignore the fact that obesity rates have closely paralleled the decline in average nightly sleep during the latter portion of the 20th century. Evidence suggests that during the 1960s, Americans were sleeping between 8.0 and 8.9 h per night (Kripke et al., 1979). By the mid 1990s, average sleep had declined to about 7.0 h (Gallup Organization, 1995), and recent data from 2005 suggest that most Americans are now sleeping less than 7 h per night (National Sleep Foundation, 2005). In fact, a 2012 report by the Center for Disease Control and Prevention (CDC) found that one in three workers now report that they routinely sleep six or fewer hours nightly (Center for Disease Control and Prevention, 2012). Shorter sleep duration is related to a variety of health problems including obesity (Patel et al., 2008). Moreover, short sleep duration earlier in life is related to increased risk of weight gain later in life (Gangwisch et al., 2005; Hasler et al., 2004; Patel, 2009). The relation between sleep and weight gain is poorly understood, but may prove crucial to stopping or even reversing the current trends.

Notably, the epidemic of obesity has particularly affected women. Epidemiological studies suggest that for the past few decades, women have shown significantly higher rates of obesity compared to men (Ogden et al., 2012), and extreme levels of obesity (i.e., Body Mass Index > 40) are more than twice as prevalent among women than men (Ogden et al., 2006). It has also long been known that women tend to be at much greater risk for developing a number of different eating related problems and clinical eating disorders relative to men (Lewinsohn et al., 2002; Striegel-Moore and Bulik, 2007; Striegel-Moore et al., 2009). While the reasons for the gender differences in eating disorders are not fully understood, some evidence suggests that there may be some cognitive and behavioral differences in responses to food, with women more frequently reporting a greater perception of loss of control over the amount of food consumed during meals (Striegel-Moore et al., 2009). Functional neuroimaging studies have also suggested that there may be sex differences in responses of key appetite regions to images of food (Killgore and Yurgelun-Todd, 2010). Interestingly, the reported sex differences in food consumption...
also appear to be mirrored in the frequency of some sleep-related complaints and disorders. For instance, a recent meta-analysis of studies of insomnia showed that women were over 1.4 times more likely to suffer from insomnia compared to men (Zhang and Wing, 2006). Although sleep apnea is more common among middle to older age men (O’Connor et al., 2000), general non-respiratory sleep complaints such as poor sleep quality, longer sleep onset latency, and difficulty with sleep maintenance tend to be more common among women in the same age range (Middelkoop et al., 1996). A recent poll by the National Sleep Foundation reported that 67% of women experience sleep problems at least a few nights each week and 46% report that they suffer from sleep problems every night (National Sleep Foundation, 2007). Thus, over the past few decades, sleep duration has declined while obesity has increased, and these problems appear to be particularly common among women.

Most studies linking insufficient sleep to excess food consumption and weight gain have emphasized the effects of sleep loss on physiological variables such as reduced energy expenditure and alterations in the hormones leptin and ghrelin, which are key regulators of appetite (Knutson et al., 2007; Patel and Hu, 2008). However, lack of sleep can affect other systems that play a role in food intake as well. For instance, sleep loss is associated with altered functional activity within a number of brain regions. Of particular relevance to food consumption is the prefrontal cortex, particularly the ventromedial prefrontal cortex (vmPFC), a complex brain region that is particularly important for evaluating the reward value of objects (Paulus and Frank, 2003), regulating emotional responses (Harari et al., 2003), and controlling behavior (Blasi et al., 2006; Ridderinkhof et al., 2004). Sleep loss is associated with a number of changes in the vmPFC, including reduced glucose metabolism (Thomas et al., 2000; Wu et al., 2006), altered functional responses during risky decision-making (Venkatraman et al., 2007) and judgments of economic value (Libedinsky et al., 2011; Venkatraman et al., 2011), as well as reduced functional connectivity with other brain regions important for self-referential and emotional processing (De Hasavas et al., 2012; Killgore et al., 2012c; Samann et al., 2010; Yoo et al., 2007). When sleep is lacking, these prefrontal changes appear to contribute to deficits in decision-making and inhibitory control (Drummond et al., 2006; Harrison and Horne, 2000; Killgore, 2010). Interestingly, recent data suggest that general daytime sleepiness is associated with reduced gray matter volume within the vmPFC (Killgore et al., 2012b). Some of these same sleep-sensitive prefrontal systems have previously been shown to be critical in responding to the calorific content of visually presented food stimuli (Killgore and Yurgelun-Todd, 2005b; Killgore et al., 2003) and may even relate to greater body mass index (BMI) (Killgore and Yurgelun-Todd, 2005a). Thus, evidence suggests that insufficient sleep alters functioning in key brain regions that are particularly responsive to the calorific content of food and which are important for regulating and inhibiting behavior.

The goal of the present study was to examine the relation between self-reported general daytime sleepiness and prefrontal cortex responses to the calorific content of food images. Based on the neuroimaging and behavioral literature outlined above, we hypothesized that greater general daytime sleepiness would be associated with reduced functional responsiveness of the vmPFC to high- versus low-calorie food images, and that the magnitude of responsiveness within this inhibitory region would predict self-reported problems with overeating. Furthermore, given the sex differences in the current rates of obesity, eating disorders, and sleep complaints, we also hypothesized that the relationships would be stronger in women than in men.

Methods

Participants

Thirty-eight healthy right-handed adults, ranging in age from 18 to 45 years (16 women, 22 men), were recruited via flyers and internet advertisements posted around Boston, MA, and the surrounding areas. Participants were thoroughly screened by a trained research technician during a semi-structured interview. Based on this screening, enrolled participants were deemed to be free of any evidence or history of severe medical conditions, head injury, loss of consciousness > 30 min, brain tumors, seizures, neurologic conditions, symptoms consistent with Axis I psychopathology, or drug or alcohol treatment. Additionally, potential participants were excluded for current or recent use of any psychoactive medications or illicit substances, or excessive alcohol intake. Table 1 provides basic demographic information for the women and men separately. Body mass index (BMI) ranged from normal (19.80) to moderately obese (34.78) for the sample as a whole (M = 24.60, SD = 3.75), but this did not differ between women and men (see Table 1). Each participant completed detailed logs of all food consumed on the day of the scan. Two independent raters used the food logs to calculate each participant’s calorie consumption during the hours preceding the scan via a primary web-based resource for determining calorie content from foods (http://ndb.nal.usda.gov), and relied on a secondary resource when a definitive answer could not be obtained from the first (http://caloriecount.about.com). Inter-rater reliability in calorie scoring was extremely high (ICC = 0.97, CI = 0.95–0.98), and the independent ratings were averaged for each participant to obtain a final estimate of total calorie consumption. On the whole, participants consumed an average of 327.8 calories (SD = 243.6) during the hours leading up to the scan, with no significant difference between women and men in calorie intake (see Table 1). Overall, typical caffeine use was modest, ranging from 0 to 444 mg per day (M = 104.08, SD = 117.65), and did not differ between women and men. Similarly, caffeine use on the day of the scan was not significantly different for the women and men. Participants reported generally normal amounts of weeknight sleep (M = 7.36, SD = 0.88 h) and weekend sleep (M = 7.71, SD = 1.32 h), as well as normal amounts of sleep the night before the scan (M = 7.04, SD = 1.02 h).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and performance variable information for participants.</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Men (n = 22)</td>
<td>Women (n = 16)</td>
</tr>
<tr>
<td></td>
<td><strong>M</strong> SD</td>
<td><strong>M</strong> SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.50 9.30 28.25 7.48</td>
<td>31.09 9.80 27.08 7.84</td>
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<tr>
<td>BMI (weight [kg]/[height [m]^2])</td>
<td>24.24 3.60 25.08 4.01</td>
<td>24.17 3.20 24.85 4.20</td>
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<tr>
<td>Pre-scan calories consumed</td>
<td>358.8 236.7 285.1 254.1</td>
<td>358.6 236.7 285.1 254.1</td>
</tr>
<tr>
<td>Typical caffeine use (mg/day)</td>
<td>101.94 127.48 107.02 106.64</td>
<td>101.94 127.48 107.02 106.64</td>
</tr>
<tr>
<td>Study day caffeine use (mg)</td>
<td>73.96 122.17 88.91 106.27</td>
<td>73.96 122.17 88.91 106.27</td>
</tr>
<tr>
<td>Weeknight sleep (h)</td>
<td>7.36 0.94 7.36 0.81</td>
<td>7.36 0.94 7.36 0.81</td>
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<tr>
<td>Weekend sleep (h)</td>
<td>7.82 1.31 7.56 1.38</td>
<td>7.82 1.31 7.56 1.38</td>
</tr>
<tr>
<td>Last night sleep (h)</td>
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<td>6.91 0.97 7.22 0.93</td>
</tr>
<tr>
<td>ESS</td>
<td>5.77 3.74 5.31 3.18</td>
<td>5.77 3.74 5.31 3.18</td>
</tr>
<tr>
<td>Current hunger (1–7)</td>
<td>4.64 1.33 5.00 1.41</td>
<td>4.64 1.33 5.00 1.41</td>
</tr>
<tr>
<td>Typical appetite (1–10)</td>
<td>6.18 1.40 6.63 1.45</td>
<td>6.18 1.40 6.63 1.45</td>
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<tr>
<td>Eat more than intended to eat (1–10)</td>
<td>3.55 1.01 5.06 1.24</td>
<td>3.55 1.01 5.06 1.24</td>
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<tr>
<td>Flower picture ratings</td>
<td>1.00 0.16 1.01 0.04</td>
<td>1.00 0.16 1.01 0.04</td>
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<tr>
<td>Low-calorie picture ratings</td>
<td>3.63 1.35 3.83 1.36</td>
<td>3.63 1.35 3.83 1.36</td>
</tr>
<tr>
<td>High-calorie picture ratings</td>
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<td>4.33 1.26 4.13 1.19</td>
</tr>
<tr>
<td>Low-calorie picture memory</td>
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<td>0.75 0.15 0.80 0.07</td>
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<tr>
<td>High-calorie picture memory</td>
<td>0.77 0.14 0.84 0.10</td>
<td>0.77 0.14 0.84 0.10</td>
</tr>
</tbody>
</table>

The table shows that there are no differences between men and women on demographic and performance variables. BMI = Body Mass Index; ESS = Epworth Sleepiness Scale; Current Hunger was rated on a 7-point scale (1 = not at all hungry; 7 = extremely hungry); Typical Appetite was rated on a 10-point scale (1 = never hungry; 10 = always hungry); Eat More than Intended to was rated on a 10-point scale (1 = never; 10 = always); Ratings refer to post-scan ratings taken for each image shown in the scanner. Participants responded to the question “how much you would like to eat each item right now” (1 = do not want to eat it; 7 = strongly desire to eat it). Memory scores indicate the proportion of correct recognition responses for each category of images (i.e., previously seen versus new foils) shown during the post-scan recognition test.
SD = 0.95 h). No sex differences were observed on any of these variables (see Table 1). All participants provided written informed consent prior to enrollment and were compensated for their time. This research study was approved by the McLean Hospital Institutional Review Board.

**Materials and procedure**

Each participant arrived for the study and underwent informed consent between 9:00 and 11:00 a.m. For the remainder of the morning, participants completed several self-report inventories, including questionnaires about demographic information, sleep habits, recent sleep, caffeine use, dietary intake, and appetite. In particular, participants were asked to respond to the query “what is your appetite like?” on a 10-point scale (Appetite: 1 = never hungry; 10 = always hungry), and to respond to the query “do you feel you eat more than you intend to” on a 10-point scale (Overeating: 1 = never; 10 = always). Participants also completed the Epworth Sleepiness Scale (ESS) (Johns, 1991), a self-report measure of general daytime sleepiness. The ESS is the most widely used self-report measure of general subjective sleepiness in the world (Drake, 2011) and shows high internal consistency reliability (Cronbach's α = 0.88) as well as high test-retest reliability (r = 0.82) over five months in healthy individuals (Johns, 1992). This scale requires the respondent to rate their chance of falling asleep in eight different situations (e.g., sitting and reading; as a passenger in a car for an hour without a break) in recent times along a 4-point scale (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). Responses are summed to provide a total score (maximum: 24). Higher scores indicate greater general daytime sleepiness, and scores greater than 10 reflect excessive daytime sleepiness in the clinically significant range. Thus, the scale measures a general level of chronic propensity to fall asleep across a variety of settings rather than the acute level of sleepiness that may be measured with other state indices. This may allow greater unmasking of chronic sleep debt by focusing on the broader behavioral propensity for sleep than other measures of acute sleepiness (Pilcher et al., 2003). Participants were not restricted in their food consumption throughout the morning, but were required to document all intake for the day on a dietary log. No food was consumed within an hour prior to the functional neuroimaging scans.

Between 12:30 and 3:00 in the afternoon, participants underwent functional magnetic resonance imaging (fMRI) while completing a food perception task (FPT). The present task was a slightly modified version of the same task we have used in our prior work (Killgore and Yurgelun-Todd, 2005a,b, 2006, 2007, 2010; Killgore et al., 2003, 2010). During the FPT, participants viewed a series of 30-second blocks of images depicting high (H) calorie foods (e.g., cheesburgers, French fries, cake, ice cream, candy), low calorie (L) foods (e.g., fresh salads, fruits, vegetables, fresh fish, whole grain bread), or control (C) images (i.e., non-edible rocks, flowers, shrubs). During each block, ten images were shown for three seconds each. The task included 15 s of resting fixation (+) at the beginning and end of the scan. The total duration of the FPT was 240 s and followed a constant presentation order (+, C, L, H, C, H, L, C, +) (see Supplementary Fig. 1). Participants were given the following instruction: “For this task, you will see a series of photographs. Try your best to remember the photographs, because your memory for the pictures will be tested after the scan.”

At the conclusion of the scan, participants completed a recognition task that presented all of the previously seen food items along with an equal number of distractor items. Following the recognition task, participants completed a 7-point rating scale to indicate their current level of hunger (i.e., 1 = not at all hungry; 7 = extremely hungry), and were then shown all of the previously seen food and control images. For each image, they were asked to rate “how much you would like to eat each item right now” (1 = do not want to eat it; 7 = strongly desire to eat it).

**Magnetic resonance imaging parameters**

Participants were scanned using a 3.0 Tesla SIEMENS Tim Trio scanner and a 12-channel head coil. At the outset, structural MRI scans were collected using a T1-weighted 3D MPRA GE sequence (TR/TE/flip angle = 21.2/6.25 ms/12°) over 128 sagittal slices (256 × 256 matrix) and a slice thickness of 1.33 mm, yielding a voxel size of 1 × 1 × 1.33 mm. During the FPT, a 4-minute blood oxygenation level dependent (BOLD) fMRI was acquired over 43 transverse interleaved slices using a T2*-weighted echo planar imaging sequence (TR/TE/flip angle = 3.0 s/30 ms/90°), with 80 images per slice (3.5 mm thickness, no skip; 22.4 cm field of view; 64 × 64 acquisition matrix), yielding a voxel size of 3.5 × 3.5 × 3.5 mm.

**Image processing**

The functional data were pre-processed and analyzed using standard algorithms in SPM5 (Wellcome Department of Cognitive Neurology, London, UK). For each subject, the time series of images was spatially realigned and motion corrected, co-registered to the individual’s own anatomical image, spatially normalized to fit the template of the Montreal Neurological Institute (MINI), spatially smoothed using an isotropic Gaussian kernel (full width at half maximum [FWHM] = 6 mm), and resliced to 2 × 2 × 2 mm. Finally, the time series was also convolved with the canonical hemodynamic response function in SPM5, the effects of serial autocorrelation were removed using the first-level autoregressive model, and a high-pass filter of 128 s was used to remove low frequency drift in the signal.

**Statistical analysis**

The analysis proceeded in several stages. First, sex differences on questionnaire and behavioral indices were examined via independent samples t-tests. Next, zero-order correlations between behavioral variables, including total ESS, appetite, and overeating were examined for the sample as a whole and separately for women and men. Gender comparisons of correlations were undertaken with Fisher’s r-to-z-transformation with comparison to a directional z-distribution. Third, the functional neuroimaging data were analyzed in a multi-stage process. At the initial stage, the primary effect of the calorie conditions within the food perception task was determined. This entailed constructing a general linear model for each individual that contrasted the difference in BOLD response between the high calorie and low calorie food conditions (see Supplementary Fig. 1). These contrast images were then taken to a second level random effects analysis via the multiple linear regression module of SPM5 to examine the relationship between total ESS scores and greater responsiveness of the brain to the high calorie condition of the FPT within the vmPFC. Based on our a priori hypotheses derived from previous research on the effects of sleep loss on brain function, we restricted the primary analyses to the two bilateral search territories within a subregion of the ventromedial prefrontal cortex (i.e., left and right gyrus rectus) defined by the Automated Anatomical Labeling Atlas (Tzourio-Mazoyer et al., 2002) and implemented via the Wake Forest University PickAtlas Utility (Maldjian et al., 2003) as a toolbox in SPM5. Dilation factor of the utility was set to 0. Correlations were initially thresholded at p < .001, k (extent) ≥ 10 contiguous voxels, and then subjected to small volume correction for multiple comparisons within each search territory at p < .05, corrected for false discovery rate (FDR). Finally, to evaluate the relationship between sleepiness-related brain activation and eating behavior, mean signal intensity was extracted from each significant cluster of activation during the FPT and correlated with behavioral indices, including ratings for the items querying about typical appetite and eating more than intended. These relationships were examined separately for women and men. Differences in the magnitude of correlation coefficients between men and women were tested using the r-to-z-transformation with comparison to a directional z-distribution. A two-tailed test was performed.

No sex differences were observed on any of the behavioral variables (see Table 1). All participants provided written informed consent prior to enrollment and were compensated for their time. This research study was approved by the McLean Hospital Institutional Review Board.
Results
Sex differences in questionnaire and eating behavioral indices

As evident in Table 1, women and men showed no significant differences in demographic, sleep, or appetite variables. Critically, there also was no sex difference in calories consumed on the day of the scan. During neuroimaging, both groups attended well to the task, with men (M = 76% correct, SD = 14%; t(21) = 8.61, p < .001) and women (M = 82% correct, SD = 8%; t(21) = 16.74, p < .001) scoring significantly above chance in their recognition of the previously seen food items after the scan.

Correlations between sleepiness and self-reported appetite/overeating behavior

Simple whole brain contrasts between food and control conditions and between High and Low Calorie conditions are presented in the online Supplementary Results (see Supplemental Fig. 2, and Supplemental Table 1 and 2). For the sample as a whole, ESS scores were positively correlated with typical appetite ratings (r = .53, p = .001), suggesting that greater general daytime sleepiness was associated with greater appetite. As evident in Fig. 1, this was true for men (r = .44, p = .038), but was nonsignificantly stronger for women (r = .72, p = .002) (z = −1.21, p = .11). In contrast, ESS was not significantly correlated with the tendency to overeat (r = .18, p = .29), which did not differ for men (r = .13, p = .58) or women (r = .37, p = .16) (z = −0.72, p = .24). Similarly, ESS was not significantly correlated with current hunger at the time of the scan (r = .24, p = .14), and these nonsignificant relations were similar for men (r = .23, p = .30) and women (r = .30, p = .26) (z = −0.21, p = .42).

Correlations between sleepiness and brain responses

The correlation between ESS and brain responses to the High>Low Calorie contrast was evaluated for the entire sample as a whole. Within the search territories investigated, there were no regions that were significantly positively correlated with general daytime sleepiness scores. There was, however, a single cluster within the vmPFC that emerged as significantly negatively correlated with ESS scores. Fig. 2 shows the location of this cluster within the left gyrus rectus (MNI: x = −8, y = 40, z = −20; k = 18 voxels; p = .047 FDR small volume corrected). No other regions within the search territories were significantly correlated with ESS. To ensure that our findings were not driven by observations with extreme influence, we examined standardized residuals and leverage values. No standardized residuals exceeded 3.0, suggesting that none of the observations were extreme outliers. One observation exceeded threshold for leverage (i.e., 2(k + 1)/n > 0.105, where k = the number of predictors and n = sample size). With this observation removed, the correlation between the ESS and extracted parameter estimates for the left gyrus rectus cluster remained significant at p < .01. Furthermore, to determine whether this finding was influenced by current hunger or previous food ingestion, we correlated the mean signal intensity values of this region with these scores. Activation in this cluster was not correlated with prior calorie consumption for the sample as a whole (r = −.05, p = .79), and this was true for both men (r = −.10, p = .65) and women (r = .06, p = .84) (z = −0.45, p = .33). Similarly, mean cluster activation was not significantly related to prior calorie consumption for the sample as a whole (r = −.12, p = .46), a finding that was similar among men (r = −.13, p = .55) and women (r = −.04, p = .90) (z = −0.25, p = .40).

Fig. 1. Scatterplots showing the association between general daytime sleepiness on the Epworth Sleepiness Scale (ESS) and eating-related variables separately for men and women. Daytime sleepiness was significantly correlated with general appetite ratings for both A) men and B) women. In contrast, there was no significant correlation between general daytime sleepiness scores and the tendency to overeat among C) men or D) women.
The mean beta values from the cluster identified above were extracted for each individual and correlated with self-reported appetite and overeating behavior. For the sample as a whole, there was no significant relationship between vmPFC activation and appetite ($r = -0.22, p = 0.18$) for either men ($r = -0.29, p = 0.19$) or women ($r = -0.28, p = 0.29$) ($z = -0.03, p = 0.49$). With regard to overeating, there was also no significant relationship with the vmPFC for the sample as a whole ($r = 0.24, p = 0.14$). However, men and women appeared to differ in this response pattern (see Fig. 3). While men showed no significant association between vmPFC activation and self-reported overeating ($r = 0.10, p = 0.65$), women showed a significant negative correlation ($r = -0.52, p = 0.04$), a difference that was statistically significant ($z = 1.88, p = 0.03$), suggesting that reduced responsiveness of this region during food perception was associated with a greater tendency to eat more than intended.

Discussion

We found that self-reported daytime sleepiness was associated with several factors that could lead to excessive food consumption. First, general daytime sleepiness, as assessed by the ESS, was associated with increased ratings of global appetite. Second, when participants were confronted with images of enticing high-calorie foods during neuroimaging, general daytime sleepiness was also associated with reduced activation within a cluster located within the vmPFC, a brain region involved in the ability to inhibit and control emotions and behavior. Third, this reduction in prefrontal activation was directly predictive of self-reported difficulty curtailing food intake, although this association was only significant for women. These findings add to a growing literature suggesting that insufficient sleep and its sequelae are associated with weight gain and the development of obesity (Patel, 2009; Van Cauter and Knutson, 2008), but also sheds light on some additional neurobiological mechanisms in this process that may have heretofore been overlooked.

Recent reviews of the literature have proposed several key physiological mechanisms through which short sleep duration is likely to
contribute to increased risk for obesity and diabetes (Knutson et al., 2007; Van Cauter et al., 2008). Most current hypothesized models propose that sleep curtailment leads to 1) increased calorie intake due to alterations in the balance of appetite related hormones and more time available to eat, and 2) reduced energy expenditure due to increased fatigue and altered thermoregulation (Knutson et al., 2007; Patel and Hu, 2008). A prominent feature of these models is evidence that sleep loss exerts a powerful influence on the balance of the hormones that regulate hunger and food consumption, including the appetite stimulating hormone ghrelin and the appetite suppressing hormone leptin (Gale et al., 2004; van der Lely et al., 2004). One large scale study with over a thousand participants showed that polysomnographically measured sleep during an overnight laboratory stay was positively correlated with leptin and negatively correlated with ghrelin levels measured from blood samples the next morning (Taheri et al., 2004). In rodents, laboratory sleep deprivation leads to excessive food consumption (Rechtschaffen and Bergmann, 1995), and studies in humans also suggest that sleep deprivation leads to increased appetite, hunger (Benedict et al., 2012; Pejovic et al., 2010; Spiegel et al., 2004), total food intake (Brondel et al., 2010), and snacking on empty calories (Nedeltcheva et al., 2009). Such findings have led many researchers to suggest that these physiological changes following short sleep duration may contribute to the propensity toward overweight and obesity (Knutson et al., 2007; Patel, 2009; Patel and Hu, 2008; Patel et al., 2008; Van Cauter and Knutson, 2008; Van Cauter et al., 2008).

While physiological factors such as altered leptin and ghrelin levels and reduced energy expenditure appear to play key roles in food intake following sleep loss, the present findings suggest an additional effect of chronically insufficient sleep that may also contribute to overeating. Specifically, we found that higher levels of general daytime sleepiness, as measured by the ESS, were associated with reduced responsiveness of a small cluster within vmPFC when exposed to visual images depicting unhealthy high-calorie foods. This region of the brain has been shown to be critical to a number of emotional and behavioral functions that may directly affect appetitive behavior, including inhibitory capacity (Hodgson et al., 2002; Hornberger et al., 2011; Silbersweig et al., 2007; Sztokawska et al., 2007), representation of the affective value of stimuli (D'Addo et al., 2012), and the ability to suppress short-term gains in the service of obtaining longer-term advantageous outcomes (Bechara, 2004; Bechara et al., 2000). Damage to this region has been associated with shortened decision-making (Bechara et al., 1994) and problems inhibiting behavior (Hornberger et al., 2011; Sztokawska et al., 2007). Moreover, we found that the lower the activation within this region of the brain, the greater the self-reported tendency to overeat. Thus, not only does lack of sleep affect the metabolic energy balance and hormonal regulators that contribute to increased hunger or appetite, but general daytime sleepiness itself appears to be associated with reduced functional activation within an inhibitory brain region that is critical for regulating behavior, a decline which in turn relates to excessive food consumption.

These findings are consistent with evidence from studies of the effects of laboratory-based sleep deprivation on brain functioning and behavioral control. Studies using PET imaging have demonstrated reduced regional glucose metabolism within the vmPFC following as little as one night of sleep loss (Thomas et al., 2000; Wu et al., 2006). This alteration in brain function within inhibitory and emotional control regions following sleep deprivation corresponds with increased impulsiveness and risk-taking behavior. For example, behavioral studies have shown that sleep deprivation is associated with reduced inhibitory capacity on a go/no-go task (Drummond et al., 2006), short-sighted preference for immediate risky gains over the potential for greater long-term losses (Killgore, 2006; Killgore et al., 2012a), increased impulsive risk-taking (Killgore, 2007; Killgore et al., 2011), and a bias for risky choices when the outcome is viewed in terms of potential gains rather than losses (McKenna et al., 2007).

Overall, sleep deprived individuals tend to show a greater expectation that their risky decisions will lead to gains and a diminished expectation for losses (Venkatraman et al., 2007). Additionally, during sleep deprivation, individuals begin to shift their decision-making strategies away from a focus on avoiding losses toward one of seeking increased gains, a pattern that also involves changes in the activation of the vmPFC (Venkatraman et al., 2011). Evidence also suggests that sleep loss alters the economic value ascribed to stimuli, increasing the perceived reward value of stimuli for some individuals while decreasing it for others (Liedinsky et al., 2011), a pattern that correlates significantly with changes in the activation of the vmPFC following sleep deprivation. When interpreted in light of these prior studies, the inverse relationship between general sleepiness and prefrontal activation we observed suggests that generally sleepy individuals may experience reduced ability to inhibit impulses to eat high calorie foods or they may show increased valuation or expectation of reward from such foods relative to their less sleepy counterparts. Future research will be necessary to determine the relative contribution of prefrontal disinhibition versus altered reward value in the tendency to overeat among individuals with chronically elevated levels of sleepiness.

Interestingly, whereas greater general daytime sleepiness was associated with increased appetite ratings for both sexes, we found that the correlation between food-specific brain responses and self-reported overeating was present only among women, despite similar levels of overeating between sexes overall. These findings are consistent with recent evidence suggesting that women and men may differ in their ability to inhibit activation of the orbitofrontal cortex and suppress corresponding feelings of hunger (Wang et al., 2009). Such findings have previously been proposed as one contributing factor to the higher rates of obesity and eating disorders among women (Hoek, 2006; Striegel-Moore and Bulik, 2007; Striegel-Moore et al., 2009). Prior studies have suggested that women tend to report greater loss of control when eating (Striegel-Moore et al., 2009), a finding that comports well with our results showing that sleepiness-related reductions in prefrontal activation in women were associated with the tendency to eat more than intended. Recent research has also shown that men and women respond differently to high- and low-calorie food stimuli, with women tending to show stronger activation in the insular cortex than men in response to high calorie foods (Killgore and Yurgelun-Todd, 2010). Other studies have also suggested that women show greater activation of dorsolateral prefrontal regions to hedonic foods (Cornier et al., 2010), and greater responsiveness of visual processing regions than men when in a hungry versus sated state (Frank et al., 2010). The precise cause of these sex differences in brain responsiveness still remain elusive, but it seems likely that such distinctions may relate to differences in gonadal sex hormones, which appear to have significant effects on a number of neurological and physiological systems related to food consumption, particularly with regard to the regulation of insulin and leptin (Woods et al., 2003). Further research aimed at addressing the underlying sex differences in responses to food stimuli and the role which sleep may play in this process will be critical in addressing the urgent problem of rising rates of obesity in Western cultures.

While the present study suggests that general daytime sleepiness is related to the functioning of prefrontal regions important to behavioral control and eating behavior, several limitations of this research should be considered. First, we explored the construct of general subjective “sleepiness” rather than short sleep duration or total sleep deprivation. While sleepiness is a common outcome of insufficient sleep, the two constructs are not directly interchangeable. Second, general sleepiness on the ESS reflects a stable assessment of the propensity for sleep to occur across a variety of settings relative to “acute sleepiness” as assessed by other state measures of immediate sleepiness, which were not used here. Of course, there may be measurement error and recall biases inherent in any such subjective measure which queries about recent experience. The present findings can only be
validly generalized to general or chronic levels of sleepiness that tend to emerge with accumulated sleep debt over time, as is generally assessed with the ESS. Third, participants in this study were not selected for weight status, and we specifically screened out individuals with a history of psychopathology, including eating disorders. Consequently, these findings may not generalize to individuals with eating disorders or problems with obesity. Further research with such populations would be an important extension of this work. Fourth, based on prior research suggesting that the vmPFC may be a particularly important region affected by short sleep duration, we focused specifically on that region. Obviously, other regions or networks, such as reward circuitry, interoceptive signaling systems, emotional processing, and visual perception regions, may also be important and should be explored in future research. Fifth, our study lacked any assays for appetite-related hormones such as leptin and ghrelin, so it is not possible to directly rule out the influence of these factors on performance. Lastly, rather than having our participants follow a fasting period, we opted to have them assessed following their normal daily intake of food during the morning. Nonetheless, energy consumption was monitored closely via food logs, and no food was consumed within an hour before the scanning. Therefore, we controlled for the effects of caloric intake in our analyses, it is possible that the findings may have been different if participants were tested in a strictly fasting or satiated state. With due consideration of these potential limitations, we believe the present study provides important new data regarding the role of general daytime sleepiness in brain responses to high-calorie, unhealthy foods. These findings suggest that, in addition to the effects sleep loss on hormonal levels and energy balance, general daytime sleepiness may also affect brain regions that are critical to the ability to make effective decisions, regulate emotions, and inhibit behavior. Such altered brain functioning due to sleepiness may be an additional and potentially modifiable factor that contributes to the current epidemic of obesity. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.01.018.

Conflicts of interest
None declared.

References