ORIGINAL ARTICLE

Unrecognized Sleep Loss Accumulated in Daily Life Can Promote Brain Hyperreactivity to Food Cue

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Epidemiological studies have shown that sleep debt increases the risk of obesity. Experimental total sleep deprivation (TSD) has been reported to activate the reward system in response to food stimuli, but food-related responses in everyday sleep habits, which could lead to obesity, have not been addressed. Here, we report that habitual sleep time at home among volunteers without any sleep concerns was shorter than their optimal sleep time estimated by the 9-day extended sleep intervention, which indicates that participants had already been in sleep debt in their usual sleep habits. The amygdala and anterior insula, which are responsible for both affective responses and reward prediction, were found to exhibit significantly lowered activity in the optimal sleep condition. Additionally, a subsequent one-night period of TSD reactivated the right anterior insula in response to food images; however, the activity level of amygdala remained lowered. These findings indicate that (1) our brain is at risk of hyperactivation to food triggers in everyday life, which could be a risk factor for obesity and lifestyle diseases, and (2) optimal sleep appears to reduce this hypersensitivity to food stimuli.

Statement of Significance

Previous studies of neuroimaging have utilized acute sleep deprivation as a model of sleep loss, which does not necessarily reflect everyday sleep patterns. In the present study, we focused on "potential sleep debt", to estimate the underlying sleep loss in seemingly "normal" sleep habits. To measure the brain responses toward food in daily sleep loss, brain activity toward food images was compared after recovering from potential sleep debt by fulfilling the individual optimal sleep time. Increased activation in the food-related regions was identified in daily sleep conditions, without any self-reported complaints of sleep disturbances. This demonstrates the implicit brain hyperreactivity to food triggers even with no awareness of sleep loss in daily life.

Keywords: Neuroimaging, Obesity, Sleep Deprivation, fMRI, Amygdala, Insula, Potential Sleep Debt, Food.

INTRODUCTION

According to a number of studies worldwide, habitual sleep insufficiency in modern social life is a global issue.[1–7] Insufficient sleep is known to cause various public health problems such as metabolic syndrome,[8] cardiovascular disease, and lifestyle diseases such as diabetes.[9,10] There has been much interest in the suggestion that lack of sleep can be a risk factor for weight gain and obesity,[11–14] which are significant public health concerns.[15–18] Alongside the rise in obesity, the number of individuals obtaining the recommended 7 to 8 hours of sleep has been declining, with many sleeping less than 6 hours per night.[12]

Epidemiological and experimental evidence shows that sleep debt both increases appetite and enhances actual food intake.[12–14,19–23] The association between insufficient sleep and higher body mass index (BMI) is also driven by changes in satiety and hunger hormones.[23] For instance, insufficient sleep leads to an increase in blood pressure and blood cortisol, sympathicotonia, higher circulating levels of the hunger-stimulating hormone ghrelin, and decreased levels of the satiety hormone leptin.[14,24–29] Furthermore, Zheng et al.[30] imply that the hedonic component of food intake (eg, liking or pleasure) triggers energy consumption and causes an additional increase in sensitivity of the reward system to food. These vicious cycles may contribute to the pathophysiology of obesity due to lack of sleep. Recent studies have shown that levels of circulating endocannabinoids, which are known to be involved in the hedonic control of food intake, increase with sleep restriction,[31] while sleep extension decreases appetite for rewarding food (eg, sweet and salty foods).[32]

Neuroimaging techniques are considered effective for clarifying the etiological basis of hedonic eating, as hedonic eating is reportedly accompanied by addiction-like brain changes such as enhanced mesolimbic dopamine activity.[33] There have been a handful of functional neuroimaging studies focused on the neural correlates between sleep debt and obesity, mostly indicating greater activation of the reward system in response to food images when sleep is deprived.[34–37] These findings could explain why people with irregular or poor-quality sleep (eg, night-shift workers) are more prone to weight gain than those with normal sleep-wake patterns.[38,39]

However, these neuroimaging studies were carried out by manipulative restriction of sleep, such as total sleep deprivation (TSD) or severe restriction of participants' sleep time, both of which are rarely experienced and would generally be short lasting if encountered in daily life. Therefore, the findings of previous studies do not necessarily reflect habitual sleep debt, which reportedly contributes to obesity.[11–14]

Given the widespread shortage of sleep time among healthy people, it is possible that chronic sleep debt due to daily short sleep may implicitly lie even in those who do not recognize any sleep-related problems. Indeed, previous experimental research has shown that sleep sufficiency varies between individuals: even without self-reported sleepiness, some had a potential sleep debt that required a few nights of sufficient sleep time to recover from after it had implicitly accumulated in their usual sleep habits.[40]

The accumulated evidence warrants an exploration of whether potential sleep debt in habitual sleep settings promotes obesity.

We propose a novel hypothesis that individuals accumulate unrecognized sleep debt due to their seemingly normal/regular sleep habits, leading to brain hyperreactivity to food triggers. To test this hypothesis, we used functional magnetic resonance imaging (fMRI) to measure brain activity in response to food image stimuli when participants had been under their everyday sleep-wake cycle in regular social settings. Specifically, we evaluated activity in emotional, gustatory, or reward-related brain areas as reported in previous studies using food image stimuli—such as the insula, amygdala, and orbitofrontal cortex[34–37]—in conditions of habitual sleep status versus experimentally "compensated" sleep status. Participants also underwent an additional one-night TSD after their sleep debt had been corrected, to enable comparison of three different brain responses to food stimuli: reactivity in habitual sleep session (HS, the day of arrival at the lab); in the last day of 9-day extended sleep session (ES9); and after TSD (Figure 1).

EXPERIMENTAL PROCEDURES

Methods and Materials

The authors declare that all experiments on human participants were conducted in accordance with the Declaration of Helsinki and that all procedures were carried out with the adequate understanding and written consent of the participants.

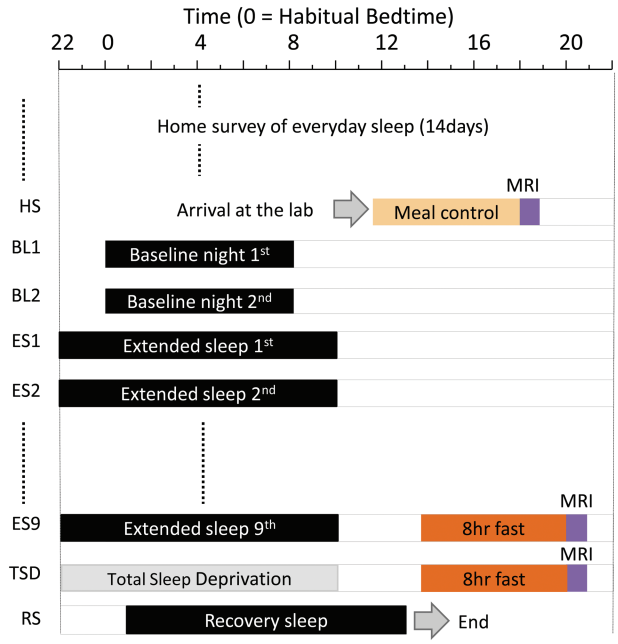

Figure 1—Schematic representation of the experimental protocol. The study included a 14-day in-home survey, habitual sleep session (HS), two 8-hour adaptation nights, baseline night (BL1, BL2), nine nights of extended sleep session (up to 12 hours) (ES1–ES9), one night of total sleep deprivation (TSD), and one recovery sleep (RS). Each bar in the timeline indicates either of a sleep period (black), one-night total sleep deprivation (gray), fasting period (orange), or MRI session (purple). Experimental tasks in the MRI scanner were done between 20:00 and 24:00. MRI = magnetic resonance imaging.

The study was approved by the Ethics Committee of National Center of Neurology and Psychiatry (Kodaira, Tokyo).

Participants

Sixteen healthy right-handed male participants (mean ± standard deviation [SD] age = 23.4 ± 2.5 years) were recruited by advertisements. One participant was excluded from the study due to withdrawal. The final number of participants was 15 (mean ± SD age = 23.3 ± 2.1). They received monetary compensation for their participation.

Eligibility requirements were age of 20–29 years, male sex (because of variation in food intake across the menstrual cycle in women), right handedness, and BMI from 18.5 to 25 kg/m^2. Individuals were excluded on the basis of the following criteria: irregular sleep/wake habits (eg, shift workers), insomnia, sleep apnea syndrome, daytime sleepiness, travel history to countries with 6-hour time differences in the 3 months preceding the study, faddy eater, vegetarian, current dieting efforts, metabolic disorders (eg, hyperlipidemia or hypercholesterolemia), psychiatric disorders, and difficulties in abstaining from smoking. Participants were also screened to rule out those who fulfilled standard MRI exclusion criteria (eg, nonremovable metal parts in/on the body, known neurological diseases, claustrophobia). All participants were confirmed to be healthy on the basis of questionnaires, examination by a physician, blood tests, T1 structural brain imaging, and all-night polysomnography recordings.

Participants had originally been recruited for a study of individual potential sleep debt[40] and completed the same interventional protocol. In the present study, however, we focused on completely different aspects of the data by adopting a neuroimaging technique to assess participants' neural responses to food stimuli in different sleep conditions. The analyses reported here do not overlap with those reported elsewhere.

Procedures for Sleep Control

Participants completed a 28-consecutive-day experiment consisting of a 14-day in-home observational period and a 14-day in-lab experimental period. During the observational period, participants wore a wrist actigraph (MicroMini-Motionlogger Actigraph, Ambulatory Monitoring Inc., Ardsley, NY) on their nondominant hand to monitor sleep schedule; accuracy was confirmed with an online sleep diary. An online visual analog scale (VAS) was also used to assess participants' sleepiness, tiredness, mood, and appetite before bedtime and to assess their self-reported sleep quality, sleepiness, mood, and appetite after waking.

All in-lab procedures during the experimental period were done in the isolation laboratory at the National Center of Neurology and Psychiatry, which enables highly advanced research on sleep-wake mechanisms and biological rhythms (http://labo.sleepmed.jp/english/facilities.html). The timing of each event in the lab was reset to the relative time, such that 0:00 corresponded to the average in-home bedtime for each individual. Participants entered the lab at 17:00 on the first day, and lights were turned off at 0:00 after a meal and a bath. For the first two nights, time in bed was set to 8 hours, starting at each individual's in-home bedtime. The first night was intended for adaptation to the lab; all data collected on this night were excluded from the analyses because sleep polysomnographic

studies have shown that it inevitably has a longer awake period ("first-night effect," see.[41]) The second night was also intended for further adaptation to the lab, and set as the "Baseline-night."

The third through 11th nights were named "Extended Sleep" (ES), and the third and 11th nights denote the first and ninth ES (ES1 and ES9), respectively. During the ES session, participants were required to stay in bed for 12 hours and could sleep as needed; thus, no participant slept more than 12 hours throughout ES. Bedtime was set 2 hours earlier than each individual's habitual bedtime to adjust the center of sleep phase between HS and ES and to cancel out the circadian effects on appetite and related brain functions as much as possible. After waking from ES9, participants entered 39 hours of TSD. For their safety, the experiment ended with a recovery sleep following TSD.

Throughout the in-lab experimental period, the room lights, participants' sleep time, temperature, and food intake (calories, amount, and time) were strictly controlled by trained technicians. Each participant was isolated in an individual compartment and prohibited from using mobile phones or the Internet to make contact with the outside.

During the sleeping phase, participants were requested to sleep on the bed in their individual compartment, where the lights were turned off (0 lx). During the waking phase, lights were set to 100 lx and participants were monitored to prevent them from falling asleep by the experimenters. Participants were permitted to move freely around the sleep lab, read, write, listen to music, watch videos, play video games, and chat with the experimenters. Room temperature and humidity were kept within 25 ± 0.5°C and 50 ± 5% relative humidity, respectively.

Control Over Dietary Intake

To help control weight, energy expenditure, and appetite throughout the experiment, the calorie content of participants' meals was determined according to their individual weights. Daily energy intake was calculated according to age-based basal metabolism, weight, and physical activity level. The index for physical activity level was set at "low" (level I = 1.5 MET [metabolic equivalents]) as the participants were restricted to the laboratory. The standard value of basal metabolism for individuals in their 20s is 24.0 kcal/kg/day; thus, the equation for individual calorie intake was as follows: (daily energy intake) = (basal metabolism standard value) × (weight) × (physical activity level). Except for one participant who did not eat a carbohydrate-containing food on the last day, participants had no leftovers that would reduce calorie intake. Mealtimes were set at 12:00, 16:00, and 20:00 (at each participant's relative time) across the experimental period, except for on days 12 and 13. On these days, meals were provided only at 12:00 and 21:00 in order to preserve an 8-hour fast prior to the fMRI scanning sessions, as suggested in a previous study.[42] To maintain a consistent daily calorie intake, the amount of calories in each meal was higher on fMRI scanning days. This was because, on scanning days, participants were restricted to two meals a day so that they would be able to fast for 8 hours before scanning. Throughout the experiment, participants' sleep status was monitored using polysomnography by experimenters who were blinded to the experimental conditions.

MRI Scanning Protocol

To assess how sleep modulation would change brain activity in response to food stimulation, participants were examined by fMRI three times: on the first day (HS), after 9 days of extended sleep (ES9), and after one night of TSD. All functional scans were done consistently before a meal, at 20:00 (relative time for each participant).

Preparation of Stimuli for fMRI

The stimulus images were 216-color pictures of food or nonfood items. Food images were selected from a calorie-counting book[43] and online materials. Nonfood images were selected from online materials. Each food image illustrated either a high-calorie food (eg, beefsteaks and hamburgers) or low-calorie food (eg, salads and pickles). Nonfood images showed neutral and nonevoking commodities (eg, pens and paper clips). Each stimulus set (high-calorie food, low-calorie food, or nonfood) contained 72 images (Figure 2). All stimulus images were modified for consistency in size, resolution, complexity, contrast, and luminance.

Stimulus Presentation Procedure

All 216 images were presented only once across all scanning sessions. Participants underwent six fMRI sessions, with two sessions each conducted during HS, ES9, and TSD. In each session, participants were exposed to 36 images: 12 of high-calorie food, 12 of low-calorie food, and 12 of nonfood items. Each image was presented for 6 seconds following presentation of a fixation cross whose duration varied from 3–9 seconds. The participants' task in the MRI scanner was to look at the images and rate how much they desired the target item using a four-point Likert scale (1 = don't want at all, 2 = slightly want, 3 = want, and 4 = strongly want). The stimulus presentation time (6 seconds) consisted of two parts: during the first half (3 seconds), participants were asked to observe the stimulus; during the last half (3 seconds), the rating scale (1–4) appeared beneath the image and participants were required to rate their desire for the target.

After each session, participants rated their sleepiness with the Stanford Sleepiness Scale[44] and were asked to report (1) whether they had fallen asleep during the scanning session and (2) their estimated percentage of sleep time. We confirmed that none of the participants fell asleep during the scan.

Analysis of Individual Desire to Food Images

Participants' desire for food and nonfood items was assessed in three different sleep conditions (HS, ES9, and TSD); therefore, we compared the scores with 2 (Food/Non-Food) × 3 (HS/ES9/TSD) repeated measures analysis of variance (ANOVA). p values < .05 were considered statistically significant. We used SPSS version 19 (SPSS Inc., Chicago, IL) for the statistical analyses.

Analysis of Individual Appetite Levels

We measured participants' appetite levels before and after breakfast on each experimental day using a VAS. Participants were asked to rate on a scale from 0 to 100 how hungry they felt before breakfast and how satiated they felt after breakfast. Note that participants received a larger breakfast on the scanning

days to maintain a consistent daily caloric intake despite receiving only two daily meals instead of three (as mentioned above, an 8-hour fast occurred before each scanning session, and so participants received one fewer meal on scanning days). This ensured that the participant hunger level would not be affected by their total calorie intake. We could thus not use the satiety data from ES9 but instead used the average of days ES7 and ES8. We hypothesized that in ES, compared with that in HS, the hunger level would decrease and the satiety level would increase. We also measured appetite level before scanning to confirm that it was controlled across sleep conditions.

fMRI Data Acquisition

A Siemens Magnetom Verio 3T MRI system equipped with a head coil was used to acquire an anatomical volume image and functional MR images of each participant. To obtain a reference image for analysis, a structural image (T1-weighted magnetization-prepared rapid gradient-echo) was taken with the following sequence parameters: repetition time (TR)/echo time (TE) = 1900/2.52 ms, voxel size = 1 × 1× 1 mm, flip angle = 9°, and field of view = 250 × 250 mm. To obtain task-related fMRI images, parameters for single-shot echo-planar imaging were set at TR/TE = 3000/30 ms, 40 axial 3-mm slices with 0.6-mm interslice gap, voxel size = 3.6 × 3 × 3 mm, flip angle = 90°, matrix size = 64 × 64, and field of view = 192 × 192 mm. Images were angled along a line connecting the anterior and posterior commissures. A total of 158 volumes were obtained during each session.

Preprocessing of fMRI Data

The first five volumes were discarded for each session to allow longitudinal magnetization to reach equilibrium. All analyses of the imaging data were performed using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, United Kingdom). Spatial realignment was done to correct head movements. Images were then warped into the Montreal Neurological Institute (MNI) standard template space and were interpolated to 2 × 2 × 2 mm voxel size. Finally, images were smoothed using a 6 × 6 × 6 mm full-width at half-maximum isotropic Gaussian kernel.

General Linear Model Analyses of fMRI Data

The first-level statistical analyses were performed using a general linear model (GLM). Four vectors of stimulus onsets were created for each condition (high-calorie food, low-calorie food, nonfood, and no response) and convolved using the canonical hemodynamic response function with the 0-second duration. In the GLM analysis, a 128-second temporal high-pass filter was applied to the data to remove low-frequency artifacts, six realign parameters were entered as nuisance regressors for movement correction. In addition, using an artifact detection toolbox (http://www.nitrc.org/projects/artifact_detect/), the scans when the participant moved more than 2 mm were regressed out with finite impulse response model in the GLM.

Estimation of the GLM model produced a brain map of parameter estimates for each condition. The high- and low-calorie food maps were collapsed (averaged) to create the individual map for food. We then created an individual contrast map for "food versus nonfood" across two sessions in each sleep condition.

Definition of Regions of Interest

We adopted a region of interest (ROI) approach for between-subject analyses of fMRI data, focusing on brain regions that are reported to be specifically activated by food cues. We selected the 16 MNI coordinates (x, y, z; mm) reported as food-related regions in a meta-analysis[45] of neuroimaging studies using food stimuli,[42,46–58] where the coordinates of these regions were worked out using activation likelihood estimation.[59]

We applied small volume correction (SVC) to the analyses of "food versus nonfood" across the three sleep conditions in our study, and we searched for significant clusters in 7-mm spheres centered on the 16 a priori coordinates reported in the previous meta-analysis. Statistical threshold for this SVC within each ROI was set to $pc < .05$, corrected with family-wise error (FWE). Because we repeated similar SVC analyses 16 times, we further confirmed the statistical validity of these analyses in terms of correction of multiple comparisons; more specifically, we additionally applied false discovery rate (FDR) correction (with the threshold set at $p < .05$) over the peak p values of the clusters found from these 16 ROI analyses. We thereby identified surviving regions among the 16 regions, which should be responsive to food stimuli. These regions were the focus of subsequent analyses.

Next, to determine the effect of compensation of potential sleep debt on the activity in food-responsive regions, we compared the individual "food minus nonfood" contrast maps between HS and ES9 using a paired t test. This produced a t-map, which was then transformed into a z-map. We extracted significantly activated clusters in food-responsive regions by performing SVC analyses of this z-map within the 7-mm sphere centered on the peak coordinates of the food-responsive clusters. The identified clusters were regions with increased or decreased activity in ES9 compared with HS. Data were considered significant if p was less than .05 FWE and the number of continuous voxels forming a cluster was greater than 5.

To assess differential activation of food-responsive clusters between TSD and the other two sleep conditions, we then separately compared neural activity in TSD with that in ES9 and HS via paired t tests using MarsBaR software (http://marsbar.sourceforge.net). We expected that activity would increase in TSD compared with ES (which showed lower activity than that in HS). The TSD versus HS analysis was conducted using a two-tailed t-test, which allowed us to examine whether the effect of sleep deficiency in everyday life would be the same as (or different from) that in experimental TSD, in terms of neural responsivity to food.

Correlation Between Desirability and Neural Responses

To examine the effect of food ratings to the neural response, we performed a parametric modulation analysis in each session. In the first-level within-subject GLM analyses, we entered event-by-event individual desirability scores for food stimuli as the parametric modulator term. Estimation of the GLM model produced a brain map of parameter estimates for each session, then all brain maps estimated session-wise were entered into a

second-level between-subject analysis, with a statistical threshold of $p < .05$, corrected with FWE, and a cluster size of $k \geq 10$ voxels.

Further, to understand if the observed neural responses would actually reflect changes in behavior that could increase the obesity risk, we performed correlational analyses between the activation and behavioral scores across different sessions. We prepared two types of contrast images, those for high-calorie foods and those for low-calorie food, and contrasted these with nonfood. We also prepared contrasted desirability scores (high calorie minus nonfood and low calorie minus nonfood, each of which had been standardized within each session). Then, we did a whole-brain regression analysis by SPM with a statistical threshold of $p < .05$, corrected with FWE, and followed this with a food-related ROI analyses using MarsBaR with a statistical threshold of $p < .05$ in each ROI.

RESULTS

Sleep Recordings

Fifteen participants who reported no habitual sleep problems with average in-home sleep time (7.3 ± 0.3 hours) were allowed to sleep freely in the lab (up to 12 hours/day). Participants' actual sleep time initially increased, then gradually decreased until reaching the set point of their optimal sleep time: compared to HS, average total sleep time significantly increased during the ES session [t (14) = 3.00, p = .009, Table 1]. The result reflected that participants' potential sleep debt had been compensated from the beginning of ES session and the degree of their sleep sufficiency reached the plateau after that.[40]

Individual Desire for Food Images During fMRI Experiments

Our initial prediction had been that their explicit desire for food might be reduced in the ES condition. However, participants' scores of self-reported desire for food, which was inspired by food images they viewed while in the MRI scanner, did not differ across different sleep conditions [F (2, 28) = .61, p = .55; 2 (Food/Non-Food) × 3 (HS/ES/TSD) repeated measures ANOVA]. The result indicates that participants were not explicitly aware of changes in their inner desire for food across sleep conditions, at least during the fMRI experiments.

Individual Appetite Levels in the Morning

We measured participants' actual appetite levels on a scale of 0 to 100 before and after breakfast in each sleep condition. As expected, participant levels of hunger before breakfast differed between the three conditions [F (1, 14) = 4.62, p = .019, Figure 3A]. Specifically, hunger decreased on the final day of ES compared with HS [t (14) = 2.14, p = .028] but increased after one night of TSD [t (14) = 2.14, p = .016], such that we found no difference in hunger after BL1 versus one night of TSD. The increased hunger level after TSD might have been partly due to the increased energy expenditure associated with sleep deprivation (Markwald et al., PNAS 2013), however this effect was found by some studies to be quite small (Jung et al., J Physiol, 2011). Participants' satiety after breakfast was also different between the three sleep conditions [F (1, 14) = 18.87, $p < .001$, Figure 3B] and was increased on the eighth day of ES compared to HS [t (14) = 2.05, p = .003]. The result suggests that sufficient sleep would make people less hungry and more prone to feel satisfied after meals. Additionally, satiety level was higher after TSD than after ES [t (14) = 3.23, p = .006]. This result was considered inevitable because the scanning schedule required that a larger breakfast be eaten on the day after TSD to maintain daily calorie intake, which inhibited the decrease in satiety level after one-night TSD.

Individual Appetite Levels Before Scanning

Variation in morning hunger levels (as shown in Figure 3A and B) across experimental days could confound the fMRI results; for example, if differential brain activation between sleep conditions was merely a reflection of differences in self-reported or physical hunger. Thus, we had participants fast for 8 hours before fMRI scans so that their appetites would be at a baseline level during fMRI sessions. We confirmed that participant hunger levels did not differ among the three sleep conditions before scanning on each experimental day [F (1, 14) = .87, p = .43, Figure 3C], indicating that the fasting was equally effective across the three sleep conditions.

Table 1—Sleep Parameters During the Experiment.

Sleep parameters	Experimental session			
	In-home	In-lab		
		BL2	ES1	ES9
Total sleep time (h)	7.3 ± 0.3	7.4 ± 0.1	10.6 ± 0.2	8.5 ± 0.3
Duration of sleep stages (min)				
Stages I + II		276.5 ± 7.1	415.1 ± 9.5	339.6 ± 17.8
Stages III + IV (SWS)		59.2 ± 7.4	61.2 ± 7.1	55.2 ± 8.5
REM sleep		107.7 ± 7.4	159.1 ± 5	116.9 ± 4.9

Values are given as average ± SE.
BL2 = the second night in the baseline session; ES1 and ES9 = the first and ninth days in the extended sleep session, respectively; REM = rapid eye movement; SWS = slow wave sleep.

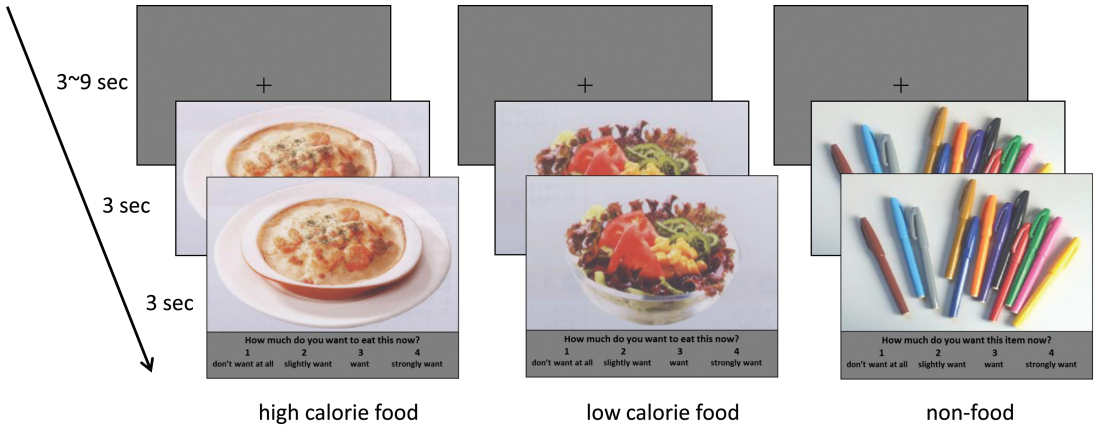

Figure 2—Stimulus images of food and nonfood. Food images contained high- and low-calorie food, and nonfood images depicted office supplies and other everyday materials. Each image was presented for 6 seconds after display of a fixation cross. Participants were asked to rate how much they desired the target using a four-point Likert scale (1 = don't want at all, 2 = slightly want, 3 = want, and 4 = strongly want).

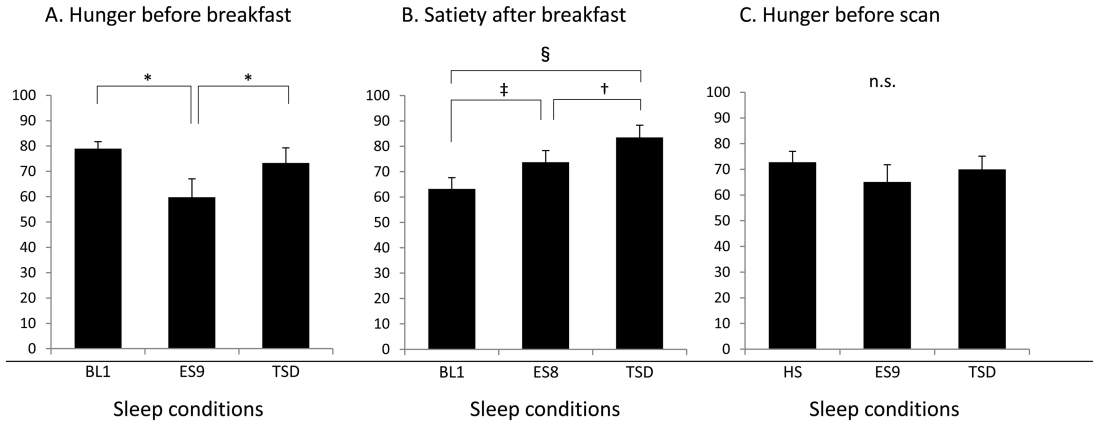

Figure 3—Appetite levels in different sleep conditions. Subjective self-evaluation scores for (A) hunger level after breakfast, (B) satiety level after breakfast, and (C) hunger level right before the scan. The scores were compared between three different sleep conditions, that is, habitual sleep session (HS), eighth/ninth night of extended sleep (ES8/9), and total sleep deprivation (TSD). Sufficient sleep decreases hunger level and increases satiety, whereas sleep deprivation increases hunger level. No significant differences were found in prebreakfast hunger levels among different sleep conditions, indicating that appetite levels before each scanning session were successfully controlled. Participant appetite levels are rated on a 0–100 visual analog scale. Error bars indicate standard errors of means. *$p < .05$, †$p < .01$, ‡$p < .005$, §$p < .001$.

fMRI Results: Identification of Food-Responsive Regions of Interest

We obtained activation maps of the three sleep conditions (HS/ES/TSD) in response to stimulus images (Figure 2) using GLM analyses. To define potential food-responsive ROIs, 16 a priori coordinates reported in the previous meta-analysis[45] were selected to apply SVC to the analyses of "food versus nonfood" across the three sleep conditions in our study (details provided in Experimental Procedures). The following 10 food-responsive regions were found to be activated by food images used in our study: the left lateral orbitofrontal cortex, centered on the coordinates (−22, 28, −16) [t (1, 42) = 4.86, p = .001]; the left anterior insula, (−32, 10, 6) [t (1, 42) = 4.8, p = .001]; the right anterior insula, (38, 6, −8) [t (1, 42) = 6.86, $p < .001$]; the left anterior insula, (−38, 2, −6) [t (1, 42) = 8.23, $p < .001$]; the left middle insula, (−36, −8, 6) [t (1, 42) = 7.84, $p < .001$]; the right middle insula, (38, −4, 10) [t (1, 42) = 9.56, $p < .001$]; the left amygdala, (−22, −2, −14) [t (1, 42) = 3.93, p = .008]; the left occipital lobe, (−20, −84, −10) [t (1, 42) = 5.35, $p < .001$]; the left lingual gyrus, (−10, −88, -8) [t (1, 42) = 7.48, $p < .001$]; and the right lingual gyrus, (12, −86, −4) [t (1, 42) = 8.47, $p < .001$] (Figure 4), all of which survived the SVC with statistical threshold of $p < .05$, corrected with FWE within each ROI, plus additional FDR correction across the 16 ROIs.

Food-Related Neural Responses After Compensation of Habitual Sleep Debt

To assess the effect of compensation of potential sleep debt on the neural response to food images, we compared the contrasted (food minus nonfood) activation of food-responsive ROIs in HS versus ES. As expected, activation decreased after ES in some

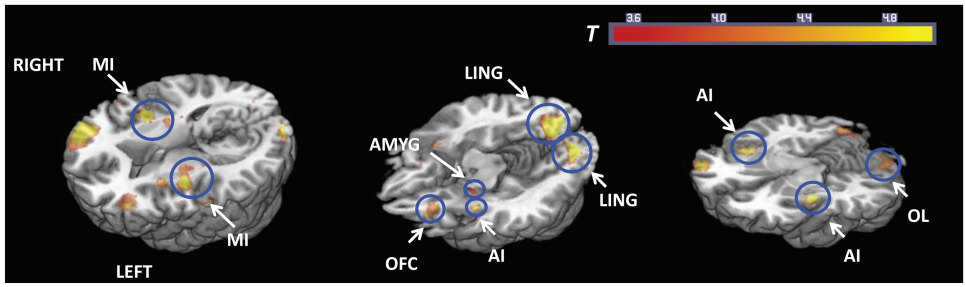

Figure 4—Brain regions responsive to food images. Activated clusters in response to the food images. Arrows indicate regions that survived small volume correction (SVC) among the food-specific regions listed in a meta-analysis.[45] AI = anterior insula; AMYG = amygdala; LING = lingual gyrus; MI = middle insula; OFC = orbitofrontal cortex; OL = occipital lobe.

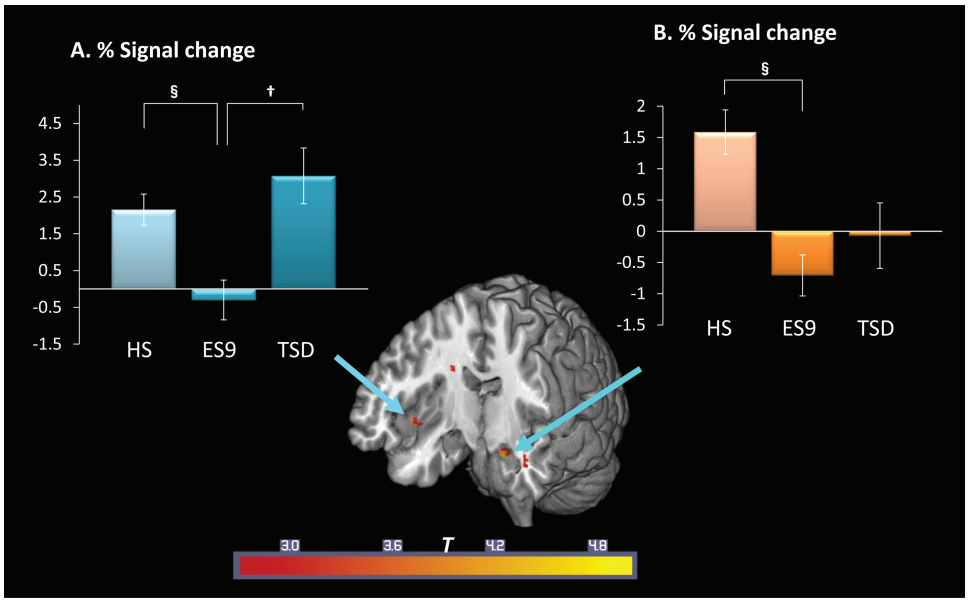

Figure 5—Brain regions with decreased activation after extended sleep. Brain regions with decreased activity in ES9 compared with HS in (A) the left amygdala (AMYG) and (B) the right anterior insula (AI). Activation after TSD varied between the two regions; the right AI shows a significant increase after TSD, but activation in the left AMYG remains stable. Error bars indicate standard errors of means. †$p < .01$, §$p < .001$. ES9 = ninth day of extended sleep; HS = habitual sleep session; TSD = total sleep deprivation.

regions among the eight ROIs: the left amygdala at (−22, −6, −18) [t (14) = 5.0, $p < .008$] and the right anterior insula at (42, 8, −6) [t (14) = 4.56, $p < .014$], with both surviving the SVC criterion (Figure 5).

Effects of TSD on Neural Responsivity to Food Cues

Our initial hypothesis was that responses lowered by ES would rebound after participants experienced one-night TSD; however, the results varied between the two regions (Figure 5). In the left amygdala, activation did not rebound after one-night TSD, instead remaining similar to activation after ES [TSD minus ES, t (14) = 1.22, p = .24] and remaining lower than activation in HS [TSD minus HS, t (14) = 2.72, p = .02]. In contrast, the response in the right anterior insula did rebound after TSD [TSD minus ES, t (14) = 3.32, p = .005], approximately to the same level of that in HS [TSD minus HS, t (14) = 1.04, p = .32].

Correlation Between Desirability and Neural Responses

Our additional parametric modulation analysis showed that activations in the following 10 regions were correlated with the desirability scores; the right lingual gyrus (14, −74, −4) [t = 13.45, k = 1427]; left postcentral gyrus (−38, −28, 60) [t = 8.89, k = 271]; left insular cortex (−40, −6, 10) [t = 8.35, k = 266]; left cuneus (−16, −96, 10) [t = 8.13, k = 114]; right insular cortex (38, −4, 14) [t = 7.79, k = 248]; right inferior frontal gyrus (46, 40, 8) [t = 6.68, k = 80]; left orbitofrontal cortex (−26, 36, −16) [t = 6.38, k = 44]; right cerebellum (26, −50, −20) [t = 6.02, k = 44]; left anterior cingulate cortex (−8, −12, 52) [t = 5.8, k = 24]; and left inferior frontal cortex (−38, 38, 12) [t = 5.59, k = 23].

The whole-brain regression analysis showed that the contrasted activation in the right fusiform gyrus only (26, −44, −12) was significantly correlated with the contrasted desirability scores (t = 5.58; k = 22; $p < .05$; FWE corrected). Further

food-related ROI analyses showed that activation in the amygdala (−22, −8, −18) was positively correlated with the contrasted desirability scores, t (164) = 1.84, p = .034].

DISCUSSION

Unlike previous studies that examined the effect of sleep debt by acutely and artificially restricting patients' sleep time, this study focused on whether habitual sleep may lead to hyperreactivity to foods in daily life, a phenomenon highly suspected to increase the risk of obesity and lifestyle diseases such as diabetes.

We first satisfied individual optimal sleep time by allowing participants' sleep time to naturally extend and then compared sleep time before and after sufficient sleep. Participants' actual sleep time increased at first and then gradually decreased until it reached their optimal sleep time. As suggested in our previous report,[40] the initial increase in sleep time was a rebound from unrecognized sleep debt in daily life, and the gradual decrease represented the convergence of sleep time on the optimum. These results show that the participants were not achieving their optimal sleep time in everyday life, although importantly, they had no complaints of daytime sleepiness or sleep problems. It is often assumed that individual sleep debt can be identified by individual awareness of daytime sleepiness; however, the fact that the participants in this study had not complained of sleep-related problems indicates that unconscious sleep debt likely exists even with "normal" everyday sleep.

Accordingly, participants' appetite level changed in the ES session; hunger decreased and satiety level increased after ES compared with HS. These results are consistent with epidemiological data and previous reports showing that sleep debt elicits calorie overconsumption.[38]

The imaging results suggest that, in processing food-cue, the affective components (activation in the left amygdala and anterior insula) can be suppressed by compensating for the potential sleep debt of everyday life. The amygdala is known to play an important role in emotional reactions and is associated with prediction of rewarding stimuli, including food-related appetitive cues[45,60,61]; this is especially true of the left amygdala.[62] Thus, the ES intervention was found to effectively regulate reward-based emotional reactivity to food triggers due to everyday sleep debt. The anterior insula, extending to the fronto-opercular cortex, responds to a wide range of emotional, sensory, and cognitive tasks[63]; but more importantly, is referred to as the "ingestive cortex" because it responds to most food-relative sensory properties[64] and even food craving.[65]

The parametric modulation analysis showed that the desirability scores rated in the scanner correlated with some regions that overlap the food-related regions in the present study. This correlation shows that the neural response is reflecting the rating behaviors to each stimulus items. However, the behavioral result does not show the differences across the sleep conditions while brain activity changes upon sleep sufficiency. This dissociation of behavior and the neural activity indicates that the neural activity is more sensitive to be affected by sleep. We found from the additional regression analysis that the food images with higher desirability induced stronger activation in the fusiform gyrus. This activation may be associated with the novelty[66] that accompanies the experience of viewing images of foods with hedonic properties, such as higher calorie foods.[67] Our study supports the assumption that the affective components of food-related processes—especially the reward and sensory properties—are easily affected by sleep insufficiency. We suggest that this hypersensitivity among people with hidden sleep debt could lead to food overconsumption.

One might suppose that a one-night TSD intervention could have caused significantly increased activation of the amygdala (as reported in[35]) even after activity in both the amygdala and the anterior insula decreased by an ES intervention. In fact, the responses of these regions differed after TSD, however; amygdala activity in our study remained robustly stable and did not return to initial levels even after acute TSD, but anterior insula activation was regained after acute sleep deprivation. The difference in magnitude of the rebound after TSD between the amygdala and insula may derive from the different functions of these regions.

In general, the anterior insula is more involved in the processing of sensory information,[68] while the amygdala functions more in the affective recognition of such information.[69] In this regard, we suppose that sufficient sleep may attenuate amygdala activation and suppress the rewarding value of food stimuli, providing some resistance to acute sleep debt that may cause hyperreactivity. On the other hand, sensory representations in the insula may be more vulnerable to acute sleep debt and be easily affected by one night of TSD. This idea of sensory vulnerability in sleep deprivation is supported by studies showing that sleep deprivation promotes a lower pain threshold and increased activation of the anterior insula.[70] Additionally, greater vulnerability of the anterior insula to food response may indicate strong involvement of the insula in increasing food craving.[71]

Note that this hyperreactivity to food cues in the brain was not the product of variations in self-reported awareness or physical sensations such as hunger; because participants were equally fasted before fMRI scanning across different sleep conditions, their awareness of appetite level was experimentally set at a constant. The found fact that sleep sufficiency affects neural responsivity to food cues even without any self-reported awareness suggests that such changes may occur insidiously in the brain. Importantly, awareness of one's sense of craving plays an important role in controlling food intake and avoiding obesity. For instance, there is some evidence that obese people are unaware of their excessive food intake.[72,73] This is very consistent with the results from our study which clearly demonstrates that sleep debt–induced brain hyperreactivity to food cues could accumulate implicitly in everyday life.

Even in HS conditions, potential sleep debt may promote brain hyperactivation on exposure to food stimuli. As these stimuli increase reward value, they may cause food craving or unconscious changes in food-intake behaviors. The anterior insula, one of the food-responsive regions, plays an important role in the craving aspect of food cues.[71] Some studies have even shown higher activation of this region in obese participants.[7,42,74–76]

Limitations

In this study, we clarified the altered brain responses elicited by food cues when individual optimal sleep time is fulfilled, compared with habitual sleep patterns. However, it should be noted that our results do not reflect participants' real-world

habitual life patterns that directly link hyperreactivation in the food-related regions and increased risk of obesity. In our study, we were not allowed to take participants' individual habitual eating behaviors into account in order to control the experimental settings. For instance, their habitual calorie intake, meal timing, and nutrient balance were not considered during the experiment due to the necessity to control all participants' hunger level at the time of scanning. To assess the direct influence of hyperreactivity in the food-related regions on obesity, further studies will be essential to investigate the association of brain activity changes with their BMI, eating behaviors, or actual calorie intake which reflect individual daily life styles.

CONCLUSION

The findings of this study serve to caution modern people that accumulated unrecognized sleep debt may unconsciously activate food-related reward regions in the brain—in fact, the same regions that are activated in people with obesity. Therefore, even "normal" sleep habits in daily life may expose us to risk for food overconsumption and eventually for obesity and lifestyle diseases.

REFERENCES

1. Basner M, Fomberstein KM, Razavi FM, et al. American time use survey: sleep time and its relationship to waking activities. Sleep. 2007; 30(9): 1085–1095.
2. Bonnet MH, Arand DL. We are chronically sleep deprived. Sleep. 1995; 18(10): 908–911.
3. Breslau N, Roth T, Rosenthal L, Andreski P. Daytime sleepiness: an epidemiological study of young adults. Am J Public Health. 1997; 87(10): 1649–1653.
4. Hublin C, Kaprio J, Partinen M, Koskenvuo M. Insufficient sleep–a population-based study in adults. Sleep. 2001; 24(4): 392–400.
5. Kaneita Y, Ohida T, Uchiyama M, et al. Excessive daytime sleepiness among the Japanese general population. J Epidemiol. 2005; 15(1): 1–8.
6. Rajaratnam SM, Arendt J. Health in a 24-h society. Lancet. 2001; 358(9286): 999–1005.
7. Rothemund Y, Preuschhof C, Bohner G, et al. Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. Neuroimage. 2007; 37(2): 410–421.
8. Xi B, He D, Zhang M, Xue J, Zhou D. Short sleep duration predicts risk of metabolic syndrome: a systematic review and meta-analysis. Sleep Med Rev. 2014; 18(4): 293–297.
9. Bray GA. Medical consequences of obesity. J Clin Endocrinol Metab. 2004; 89(6): 2583–2589.
10. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010; 33(2): 414–420.
11. Chaput JP, Després JP, Bouchard C, Tremblay A. The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. Sleep. 2008; 31(4): 517–523.
12. Knutson KL, Van Cauter E. Associations between sleep loss and increased risk of obesity and diabetes. Ann N Y Acad Sci. 2008; 1129: 287–304.
13. Nielsen LS, Danielsen KV, Sørensen TI. Short sleep duration as a possible cause of obesity: critical analysis of the epidemiological evidence. Obes Rev. 2011; 12(2): 78–92.
14. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004; 141(11): 846–850.
15. Eckel RH. Familial combined hyperlipidemia and insulin resistance: distant relatives linked by intra-abdominal fat? Arterioscler Thromb Vasc Biol. 2001; 21(4): 469–470.
16. Klein S, Burke LE, Bray GA, et al.; American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2004; 110(18): 2952–2967.
17. Patterson RE, Frank LL, Kristal AR, White E. A comprehensive examination of health conditions associated with obesity in older adults. Am J Prev Med. 2004; 27(5): 385–390.
18. Tung A. The biology and genetics of obesity and obstructive sleep apnea. Anesthesiol Clin North America. 2005; 23(3): 445–61, vi.
19. Bosy-Westphal A, Hinrichs S, Jauch-Chara K, et al. Influence of partial sleep deprivation on energy balance and insulin sensitivity in healthy women. Obes Facts. 2008; 1(5): 266–273.
20. Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D. Acute partial sleep deprivation increases food intake in healthy men. Am J Clin Nutr. 2010; 91(6): 1550–1559.
21. Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr. 2009; 89(1): 126–133.
22. St-Onge MP, O'Keeffe M, Roberts AL, RoyChoudhury A, Laferrère B. Short sleep duration, glucose dysregulation and hormonal regulation of appetite in men and women. Sleep. 2012; 35(11): 1503–1510.
23. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. Obesity (Silver Spring). 2008; 16(3): 643–653.
24. Benedict C, Hallschmid M, Lassen A, et al. Acute sleep deprivation reduces energy expenditure in healthy men. Am J Clin Nutr. 2011; 93(6): 1229–1236.
25. Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD. Insufficient sleep undermines dietary efforts to reduce adiposity. Ann Intern Med. 2010; 153(7): 435–441.
26. Schmid SM, Hallschmid M, Jauch-Chara K, Born J, Schultes B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. J Sleep Res. 2008; 17(3): 331–334.
27. Spiegel K, Leproult R, L'hermite-Balériaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab. 2004; 89(11): 5762–5771.
28. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999; 354(9188): 1435–1439.
29. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med. 2004; 1(3): e62.
30. Zheng H, Lenard NR, Shin AC, Berthoud HR. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. Int J Obes (Lond). 2009; 33 Suppl 2: S8–13.
31. Hanlon EC, Tasali E, Leproult R, et al. Sleep restriction enhances the daily rhythm of circulating levels of endocannabinoid 2-arachidonoylglycerol. Sleep. 2016; 39(3): 653–664.
32. Tasali E, Chapotot F, Wroblewski K, Schoeller D. The effects of extended bedtimes on sleep duration and food desire in overweight young adults: a home-based intervention. Appetite. 2014; 80: 220–224.
33. Liu Y, Aragona BJ, Young KA, et al. Nucleus accumbens dopamine mediates amphetamine-induced impairment of social bonding in a monogamous rodent species. Proc Natl Acad Sci U S A. 2010; 107(3): 1217–1222.
34. Benedict C, Brooks SJ, O'Daly OG, et al. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. J Clin Endocrinol Metab. 2012; 97(3): E443–E447.
35. Greer SM, Goldstein AN, Walker MP. The impact of sleep deprivation on food desire in the human brain. Nat Commun. 2013; 4: 2259.
36. St-Onge MP, McReynolds A, Trivedi ZB, Roberts AL, Sy M, Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli. Am J Clin Nutr. 2012; 95(4): 818–824.
37. St-Onge MP, Wolfe S, Sy M, Shechter A, Hirsch J. Sleep restriction increases the neuronal response to unhealthy food in normal-weight individuals. Int J Obes (Lond). 2014; 38(3): 411–416.
38. Hogenkamp PS, Nilsson E, Nilsson VC, et al. Acute sleep deprivation increases portion size and affects food choice in young men. Psychoneuroendocrinology. 2013; 38(9): 1668–1674.

39. Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB. Association between reduced sleep and weight gain in women. Am J Epidemiol. 2006; 164(10): 947–954.
40. Kitamura S, Katayose Y, Nakazaki K, et al. Estimating individual optimal sleep duration and potential sleep debt. Sci Rep. 2016; 6: 35812.
41. Agnew HW Jr, Webb WB, Williams RL. The first night effect: an EEG study of sleep. Psychophysiology. 1966; 2(3): 263–266.
42. Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage. 2008; 41(2): 636–647.
43. Kagawa Ye. Shin Gaishoku/Take-out no Calorie Guedebook [The new calorie guidebook for restaurant and take-away food]. Tokyo, Japan: Kagawa Nutrition University Press; 2002.
44. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology. 1973; 10(4): 431–436.
45. Tang DW, Fellows LK, Small DM, Dagher A. Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. Physiol Behav. 2012; 106(3): 317–324.
46. Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, Calder AJ. Individual differences in reward drive predict neural responses to images of food. J Neurosci. 2006; 26(19): 5160–5166.
47. Cornier MA, Salzberg AK, Endly DC, Bessesen DH, Rojas DC, Tregellas JR. The effects of overfeeding on the neuronal response to visual food cues in thin and reduced-obese individuals. PLoS One. 2009; 4(7): e6310.
48. Frank S, Laharnar N, Kullmann S, et al. Processing of food pictures: influence of hunger, gender and calorie content. Brain Res. 2010; 1350: 159–166.
49. Führer D, Zysset S, Stumvoll M. Brain activity in hunger and satiety: an exploratory visually stimulated FMRI study. Obesity (Silver Spring). 2008; 16(5): 945–950.
50. Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Cortical and limbic activation during viewing of high- versus low-calorie foods. Neuroimage. 2003; 19(4): 1381–1394.
51. Malik S, McGlone F, Bedrossian D, Dagher A. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 2008; 7(5): 400–409.
52. Porubská K, Veit R, Preissl H, Fritsche A, Birbaumer N. Subjective feeling of appetite modulates brain activity: an fMRI study. Neuroimage. 2006; 32(3): 1273–1280.
53. Santel S, Baving L, Krauel K, Münte TF, Rotte M. Hunger and satiety in anorexia nervosa: fMRI during cognitive processing of food pictures. Brain Res. 2006; 1114(1): 138–148.
54. Schur EA, Kleinhans NM, Goldberg J, Buchwald D, Schwartz MW, Maravilla K. Activation in brain energy regulation and reward centers by food cues varies with choice of visual stimulus. Int J Obes (Lond). 2009; 33(6): 653–661.
55. Schienle A, Schäfer A, Hermann A, Vaitl D. Binge-eating disorder: reward sensitivity and brain activation to images of food. Biol Psychiatry. 2009; 65(8): 654–661.
56. Simmons WK, Martin A, Barsalou LW. Pictures of appetizing foods activate gustatory cortices for taste and reward. Cereb Cortex. 2005; 15(10): 1602–1608.
57. St-Onge MP, Sy M, Heymsfield SB, Hirsch J. Human cortical specialization for food: a functional magnetic resonance imaging investigation. J Nutr. 2005; 135(5): 1014–1018.
58. Uher R, Treasure J, Heining M, Brammer MJ, Campbell IC. Cerebral processing of food-related stimuli: effects of fasting and gender. Behav Brain Res. 2006; 169(1): 111–119.
59. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. Neuroimage. 2002; 16(3 Pt 1): 765–780.
60. LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Hunger selectively modulates corticolimbic activation to food stimuli in humans. Behav Neurosci. 2001; 115(2): 493–500.
61. van der Laan LN, de Ridder DT, Viergever MA, Smeets PA. The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues. Neuroimage. 2011; 55(1): 296–303.
62. Hamann S, Mao H. Positive and negative emotional verbal stimuli elicit activity in the left amygdala. Neuroreport. 2002; 13(1): 15–19.
63. Craig AD. How do you feel–now? The anterior insula and human awareness. Nat Rev Neurosci. 2009; 10(1): 59–70.
64. Scott TR, Plata-Salamán CR. Taste in the monkey cortex. Physiol Behav. 1999; 67(4): 489–511.
65. Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Images of desire: food-craving activation during fMRI. Neuroimage. 2004; 23(4): 1486–1493.
66. Henson R, Shallice T, Dolan R. Neuroimaging evidence for dissociable forms of repetition priming. Science. 2000; 287(5456): 1269–1272.
67. Huerta CI, Sarkar PR, Duong TQ, Laird AR, Fox PT. Neural bases of food perception: coordinate-based meta-analyses of neuroimaging studies in multiple modalities. Obesity (Silver Spring). 2014; 22(6): 1439–1446.
68. Sterzer P, Kleinschmidt A. Anterior insula activations in perceptual paradigms: often observed but barely understood. Brain Struct Funct. 2010; 214(5-6): 611–622.
69. Elliott R, Zahn R, Deakin JF, Anderson IM. Affective cognition and its disruption in mood disorders. Neuropsychopharmacology. 2011; 36(1): 153–182.
70. Busch V, Haas J, Crönlein T, et al. Sleep deprivation in chronic somatoform pain-effects on mood and pain regulation. Psychiatry Res. 2012; 195(3): 134–143.
71. Frank S, Kullmann S, Veit R. Food related processes in the insular cortex. Front Hum Neurosci. 2013; 7: 499.
72. Cohen DA. Neurophysiological pathways to obesity: below awareness and beyond individual control. Diabetes. 2008; 57(7): 1768–1773.
73. Pliner P, Iuppa G. Effects of increasing awareness on food consumption in obese and normal weight subjects. Addict Behav. 1978; 3(1): 19–24.
74. Stice E, Spoor S, Bohon C, Small DM. Relation between obesity and blunted striatal response to food is moderated by TaqIA A1 allele. Science. 2008; 322(5900): 449–452.
75. Stice E, Yokum S, Burger KS, Epstein LH, Small DM. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci. 2011; 31(12): 4360–4366.
76. Yokum S, Ng J, Stice E. Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. Obesity (Silver Spring). 2011; 19(9): 1775–1783.

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DISCLOSURE STATEMENT

All authors declare no conflict of interest associated with this manuscript.