Acute Sleep Deprivation Enhances the Brain's Response to Hedonic Food Stimuli: An fMRI Study

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Context: There is growing recognition that a large number of individuals living in Western society are chronically sleep deprived. Sleep deprivation is associated with an increase in food consumption and appetite. However, the brain regions that are most susceptible to sleep deprivation-induced changes when processing food stimuli are unknown.

Objective: Our objective was to examine brain activation after sleep and sleep deprivation in response to images of food.

Intervention: Twelve normal-weight male subjects were examined on two sessions in a counterbalanced fashion: after one night of total sleep deprivation and one night of sleep. On the morning after either total sleep deprivation or sleep, neural activation was measured by functional magnetic resonance imaging in a block design alternating between high- and low-calorie food items. Hunger ratings and morning fasting plasma glucose concentrations were assessed before the scan, as were appetite ratings in response to food images after the scan.

Main Outcome Measures: Compared with sleep, total sleep deprivation was associated with an increased activation in the right anterior cingulate cortex in response to food images, independent of calorie content and prescan hunger ratings. Relative to the postsleep condition, in the total sleep deprivation condition, the activation in the anterior cingulate cortex evoked by foods correlated positively with postscan subjective appetite ratings. Self-reported hunger after the nocturnal vigil was enhanced, but importantly, no change in fasting plasma glucose concentration was found.

Conclusions: These results provide evidence that acute sleep loss enhances hedonic stimulus processing in the brain underlying the drive to consume food, independent of plasma glucose levels. These findings highlight a potentially important mechanism contributing to the growing levels of obesity in Western society. **(*J Clin Endocrinol Metab* 97: E443–E447, 2012)**

Levels of morbid obesity are rising throughout the Western world. Although high calorie content of food and advertising play a large part, an additional factor, chronic sleep deprivation, may also contribute. Sleep deprivation has been found to stimulate appetite and actual food intake (1, 2), which might imply that humans lacking sleep are more sensitive to rewarding food stimuli. The hedonic component of food intake triggers energy consumption, and an increased sensitivity of the reward system to food may contribute to the pathophysiology of obesity (3). Functional neuroimaging studies reveal that brain changes associated with hedonic eating and obesity, *e.g.* enhanced

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Abbreviations: AAL, Anatomical automatic labeling; BOLD, blood oxygen level-dependent; fMRI, functional magnetic resonance imaging; HC, high-calorie; IBI, interblock interval; LC, low-calorie; NS, nonsignificant; TSD, total sleep deprivation.

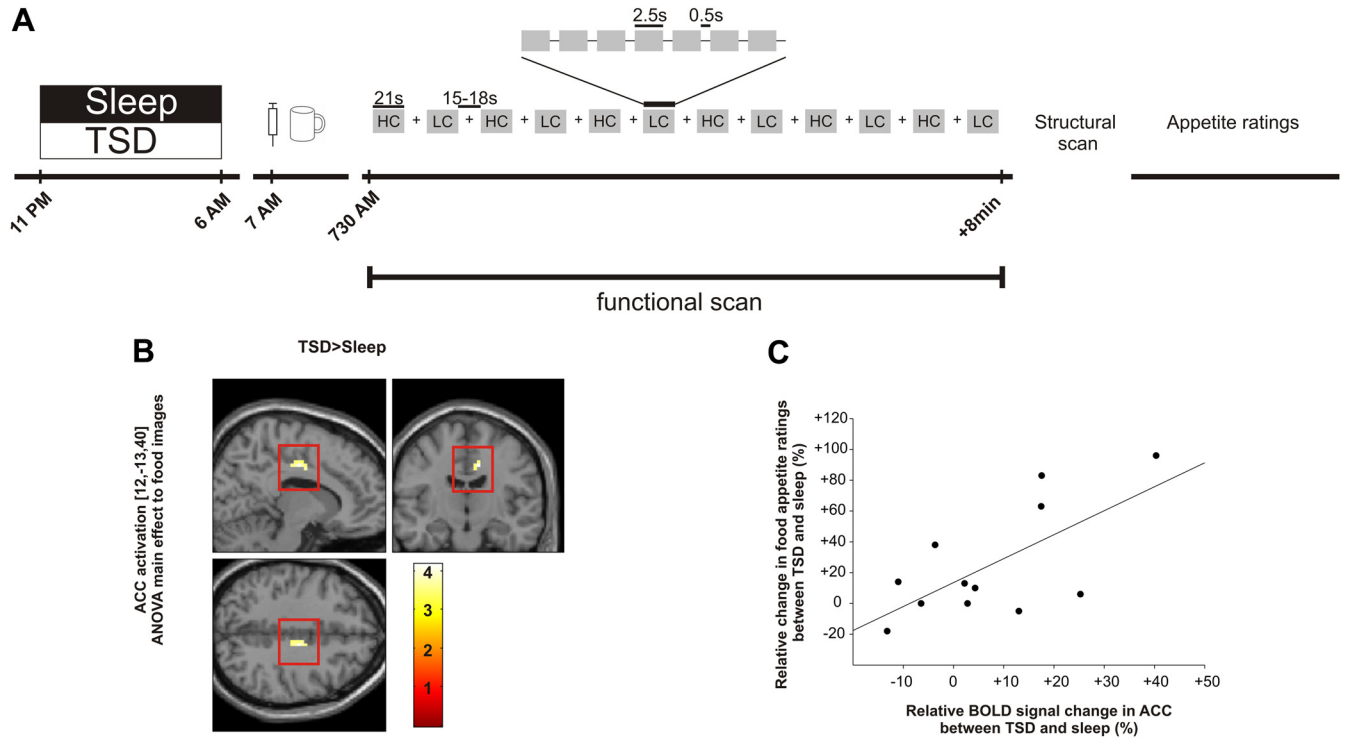

FIG. 1. TSD enhances brain activation in the right anterior cingulate cortex in response to images of foods. A, In the sleep condition, nocturnal sleep was permitted from 2300 h (lights off) to 0600 h (lights on); in the TSD condition, subjects remained awake throughout the whole experimental period. In the morning, the change in brain activation, as measured by the BOLD signal by means of fMRI, in response to alternating blocks of either HC or LC food images was recorded. Brain activation was measured after ingestion of a liquid test meal (*cup symbol*). Secondary measures were appetite ratings, prescan hunger (before and after the liquid test meal), and morning fasting plasma glucose concentration (*syringe symbol*). B, BOLD signal in response to images of foods. Rendered fMRI images of the contrast TSD *vs.* sleep for food pictures are shown. The *color bar* indicates *t* values. The peak voxel is given as MNI coordinate. C, Relative change between the conditions in anterior cingulate cortex BOLD signal plotted against the relative change in the frequency of yes responses to the question, "Do you find the food appetizing?" For this correlation analysis, the region of interest (*i.e.* the right anterior cingulate cortex) was specified from an anatomical region as defined in the AAL atlas. Pearson's r = 0.67; $P = 0.02$; n = 12.

mesolimbic dopamine activity, are also seen in addiction (4), which is characterized by compulsive reward-seeking behavior. To date, no studies have addressed whether activity of neural circuitries linked to food reward is amplified by sleep loss. Against this background, the present functional magnetic resonance imaging (fMRI) study examined brain activation after both sleep and total sleep deprivation in response to images of food. In light of previous findings suggesting a detrimental influence of total sleep deprivation on glucose metabolism (5–7), fasting plasma glucose concentration was also measured.

Subjects and Methods

Participants

Twelve right-handed, healthy, normal-weight, and medication-free men (mean ± SEM age 23.3 ± 0.6 yr and BMI 22.5 ± 0.5 kg/m^2) participated in the experiments. Individuals were excluded based on the following criteria: vegetarian, current efforts to lose weight (*e.g.* dieting), irregular meal timing habits, irregular sleep/wake habits, fell asleep during the sleep deprivation condition, and contraindications for MRI. All subjects gave written informed consent to the study that conformed to the Declaration of Helsinki and was approved by the local ethics committee.

Study design

A schematic of the experimental apparatus can be found in Fig. 1A. According to a randomized and balanced crossover design, each subject participated in two conditions [total sleep deprivation (TSD) and sleep] separated by at least 2 wk. Before sleep or TSD, subjects were provided with a standardized dinner (~700 kcal). In the sleep condition, sleep (2300–0600 h) was recorded by an ambulatory polysomnographic device (Embla Flaga hf, Reykjavik, Iceland), and sleep stages were determined according to standard criteria (8). To keep subjects awake in the TSD condition, they stayed in the laboratory and were allowed to watch TV and play board games with the experimenter, but no food was provided. The next morning at 0700 h, the subjects rated their hunger on a scale from 0 (not hungry at all) to 9 (very hungry), and their blood glucose concentration (hexokinase method, Aeroset; Abbott Diagnostics, North Chicago, IL) was measured. To minimize the potential confound of hunger evoked by TSD on brain activation in response to food images (9), our volunteers drank 350 ml curdled milk at 0710 h (~125 kcal), and their hunger was monitored again 15 min later. Subsequently, both functional and structural scans were acquired. In the func-

tional scan, a block paradigm consisting of six 21-sec epochs of low-calorie (LC) food images, and six 21-sec epochs of high-calorie (HC) food images were administered. Within each 21-sec epoch of food images, seven individual images were presented for 2.5 sec each followed by a 0.5-sec gap each, separated by a jittered (15–18 sec) interblock interval (IBI), during which a gray blank screen with a fixation cross was presented. For a detailed description of the administered food stimuli, imaging procedures, and fMRI processing, see the Supplemental Appendix (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

After the scans, each subject rated a pseudorandomly chosen subsample of 60 of the 84 images that had been presented in the scanner before (30 images each of HC and LC food). Specifically, they were asked to indicate for each food image whether they considered it to be appetizing or not by answering yes or no.

Statistical analysis

Our model encoded the two conditions of interest, namely presentation of HC and LC food pictures, with the IBI implicitly encoded. These blocks were modeled to a boxcar function and were convolved with a canonical hemodynamic response function. The data were high-pass filtered (cutoff 128 sec) and corrected for serial correlations using a first-order autoregressive model. Additionally, the model encoded volume-to-volume head movement (three translations and three rotational axes) as nuisance covariates. Contrast images for each condition (HC and LC) *vs.* the IBI were taken forward into a second level 2 × 2 analysis of covariance model. Participant's subjective hunger recorded at 0730 h (*i.e.* before the scan was performed) was entered as a covariate. Subsequently, we tested for the main effect of TSD *vs.* sleep. Results were considered significant at a P value that was <0.05 after family-wise error correction for multiple comparisons. To test our *a priori* hypothesis that TSD, compared with one night of sleep, increases the brain reward response to images of food, small-volume correction analysis was performed in brain regions that have been previously found to be activated in response to this paradigm (10). In detail, we performed small-volume correction with anatomical templates using the anatomical automatic labeling (AAL) atlas in the hippocampus, anterior cingulate gyrus, striatum, insula, orbifrontal cortex, and the prefrontal cortex. Anatomical regions of interest were defined by the AAL atlas to ensure that the selection of voxels for testing was independent of the data to be tested (11).

Behavioral data were analyzed with SPSS version 19 (SPSS Inc., Chicago, IL) by using ANOVA and specified by Student's t tests. All data are given as mean ± SEM. P values <0.05 were considered statistically significant; otherwise they were considered nonsignificant (NS).

Results

fMRI

TSD was associated with a significantly greater activation in the right anterior cingulate cortex in response to food images [Montreal Neurological Institute (MNI) coordinates [x,y,z]: [12,−13,40]; P value after family-wise error correction = 0.03 (t = 4.17); cluster size = 27, for analysis of covariance TSD/SD main effect; Fig. 1B]. During sleep there was no brain region that was significantly more activated than during TSD. Furthermore, there was no significant interaction effect between the TSD/sleep conditions and the food categories.

One concern for neuroimaging studies employing TSD is that participants may have momentary lapses in attention and alertness and may therefore close their eyes. The block design paradigm stipulated an alternation between active and resting conditions (*i.e.* food *vs.* IBI). This produced a blood oxygen level-dependent (BOLD) signal in the fusiform gyrus that was greater during the presentation of food images as compared with IBI, a pattern that did not differ between the conditions (NS for the ANOVA SD/sleep main effect).

Fasting plasma glucose and morning hunger and appetite ratings

Morning plasma glucose concentrations did not differ between the TSD and sleep conditions (4.7 ± 0.1 *vs.* 4.8 ± 0.1 mmol/liter, respectively; NS). Subjects reported significantly greater hunger after TSD than after sleep (7.4 ± 1.4 *vs.* 5.3 ± 0.8; P = 0.009). After the test meal intake but before the fMRI scan, the hunger score was lower and did not significantly differ between the conditions (TSD *vs.* sleep, 5.3 ± 0.5 *vs.* 4.2 ± 0.5; NS; P = 0.04 for the interaction between SD/sleep × time).

After the scan, sleep-deprived participants gave approximately 12% more yes responses to the question, "Do you find the food appetizing?" when they were presented with images of foods regardless of the calorie content (*vs.* sleep, 46 ± 2 *vs.* 41 ± 2 number of yes responses; P = 0.009 for the ANOVA TSD/sleep main effect). This effect was specific for HC food pictures (P = 0.001 for the interaction between TSD/sleep × food category) such that sleep-deprived subjects found approximately 24% of the presented HC pictures more appetizing than during their sleep condition (26 ± 1 *vs.* 21 ± 1 yes responses; P = 0.001), whereas no significant difference was found in terms of the number of yes responses to LC food pictures (TSD *vs.* sleep, 20 ± 2 *vs.* 20 ± 1 yes responses; NS).

Relative to sleep, in the TSD condition the BOLD response in the anterior cingulate cortex induced by food images (compared with the implicit baseline) positively correlated with postscan subjective appetite ratings (Pearson's r = 0.67, P = 0.02; Fig. 1C).

Sleep recordings

In the sleep condition, subjects were 44 ± 8 min awake and spent 10 ± 2 min in sleep stage 1, 164 ± 10 min in sleep stage 2, 115 ± 8 min in slow-wave sleep, and 50 ± 6 min in rapid eye movement sleep, respectively. The sleep-onset latency was 32 ± 9 min, slow-wave sleep latency was

12 ± 1 min, and rapid eye movement sleep latency was 129 ± 15 min.

Discussion

Here we found that, compared with one night of regular sleep, TSD was associated with increased activation of the anterior cingulate cortex in normal-weight men in response to food stimuli. This difference in anterior cingulate cortex activation positively correlated with the difference in subjective appetite ratings for the same food images presented after the scan.

The anterior cingulate cortex is a unique part of frontal cortex and plays a key role in the evaluation of different perceptual representations of food (12). Higher activation of this brain region has been found in obese compared with normal-weight subjects when anticipating food (13), suggesting that the rewarding quality of food is enhanced in obesity. A similar neural response to food images was found in the present study in normal-weight men after one night of TSD, suggesting that prolonged periods of staying awake leads to a greater reward response in anticipation of food. This view is also supported by anatomical evidence, inasmuch as the anterior cingulate cortex receives dopaminergic input via mesocorticolimbic pathways, and this afferent dopamine signaling modulates the glutamatergic projections from the anterior cingulate cortex back to the striatum (14). The striatum plays a prominent role in the regulation of hunger motivation (15).

Short sleep duration is linked to an increased risk for developing obesity, and robust evidence indicates that this primarily involves increased calorie intake (16). For instance, recurrent bedtime restriction in men increases 24-h food intake and induces subjective preferences for HC foods (1, 2). Fittingly, we show that TSD increased hunger feelings as well as appetite, especially for calorie-dense foods, which could reflect a behavior to compensate for the significantly increased energy expenditure (~7%) induced by TSD (17). Against this background, the enhanced hedonic activity in response to food images may represent a mechanism subserving the brain's energy restoration after TSD.

There are some limitations to our study. Had the paradigm been of longer duration, we may have seen differences in the brain response to HC and LC food images, as was the case for the appetite ratings. Second, we cannot rule out that the relatively short length of sleep in the sleep condition has influenced our results. Nevertheless, bearing in mind these caveats, our findings show that the neural response to rewarding food cues is sensitive to the disruption of the sleep-wake cycle, as frequently occurs, for example, in shift workers. Future research is needed to confirm our findings under conditions of partial sleep deprivation.

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References

1. **Spiegel K, Tasali E, Penev P, Van Cauter E** 2004 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 141:846–850
2. **Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD** 2009 Sleep curtailment is anterior cingulate cortex ompanied by increased intake of calories from snacks. Am J Clin Nutr 89:126–133
3. **Zheng H, Lenard NR, Shin AC, Berthoud HR** 2009 Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. Int J Obes (Lond) Suppl 2:S8–S13
4. **Liu Y, von Deneen KM, Kobeissy FH, Gold MS** 2010 Food addiction and obesity: evidence from bench to bedside. J Psychoactive Drugs 42:133–145
5. **Donga E, van Dijk M, van Dijk JG, Biermasz NR, Lammers GJ, van Kralingen KW, Corssmit EP, Romijn JA** 2010 A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. J Clin Endocrinol Metab 95: 2963–2968
6. **Schmid SM, Hallschmid M, Jauch-Chara K, Bandorf N, Born J, Schultes B** 2007 Sleep loss alters basal metabolic hormone secretion and modulates the dynamic counterregulatory response to hypoglycemia. J Clin Endocrinol Metab 92:3044–3051
7. **Benedict C, Shostak A, Lange T, Brooks SJ, Schiöth HB, Schultes B, Born J, Oster H, Hallschmid M** 16 November 2011 Diurnal rhythm of circulating nicotinamide phosphoribosyltransferase (Nampt/vis-

fatin/PBEF): impact of sleep loss and relation to glucose metabolism. J Clin Endocrinol Metab 10.1210/jc.2011-2241
8. **Rechtschaffen A, Kales A** 1968 A manual of standardized terminology, techniques and scoring system for sleep of human subjects. Washington, DC: U.S. Government Printing Office
9. **Führer D, Zysset S, Stumvoll M** 2008 Brain activity in hunger and satiety: an exploratory visually stimulated FMRI study. Obesity (Silver Spring) 16:945–950
10. **Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE** 2008 Widespread reward-system activation in obese women in response to pictures of high-calorie foods. Neuroimage 41:636–647
11. **Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI** 2009 Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 12:535–540
12. **Grabenhorst F, Rolls ET, Parris BA, d'Souza AA** 2010 How the brain represents the reward value of fat in the mouth. Cereb Cortex 20:1082–1091
13. **Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR, Butler MG, Savage CR** 2010 Neural mechanisms associated with food motivation in obese and healthy weight adults. Obesity (Silver Spring) 18:254–260
14. **Haber SN, Knutson B** 2010 The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35:4–26
15. **Rissanen A, Hakala P, Lissner L, Mattlar CE, Koskenvuo M, Rönnemaa T** 2002 Acquired preference especially for dietary fat and obesity: a study of weight-discordant monozygotic twin pairs. Int J Obes Relat Metab Disord 26:973–977
16. **Brondel L, Romer MA, Nougues PM, Touyarou P, Davenne D** 2010 Acute partial sleep deprivation increases food intake in healthy men. Am J Clin Nutr 91:1550–1559
17. **Jung CM, Melanson EL, Frydendall EJ, Perreault L, Eckel RH, Wright KP** 2011 Energy expenditure during sleep, sleep deprivation and sleep following sleep deprivation in adult humans. J Physiol 589(Pt 1):235–244