Exploring the relationships of gamma-hydroxybutyrate and sleep on metabolism, physiology, and behavior in humans

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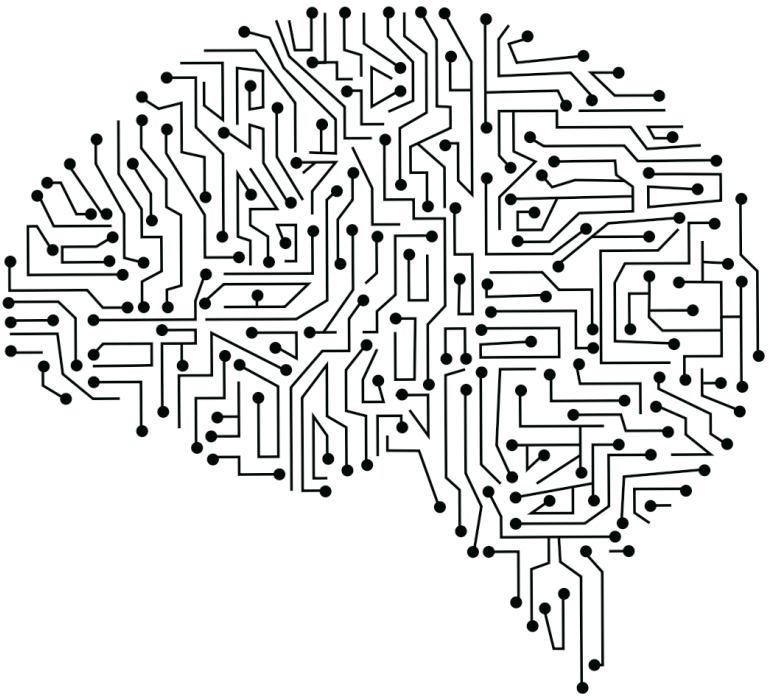
PART II

Sleep, Eating and Metabolism

CHAPTER 8

Introduction to Sleep, Eating, and Metabolism



CHAPTER 8 CONTENTS

1. Sleep and Weight

1.1 Obesity Rates Have Risen Drastically

The regulation of energy stores in the human body is maintained by a complex regulatory system involving multiple physiological pathways. In this system, peripheral signals coordinate with neural circuits to affect physiological processes and behaviors to maintain body weight within a narrow range[300–303]. Obesity, categorized as BMI equal to or over 30.0 kg/m^2, is a condition that takes place when energy intake exceeds expenditure over a prolonged period of time manifesting in excess adiposity from this chronic, positive energy balance. In the United States, between 1976 and 2008, the prevalence of obesity increased by an alarming amount[304,305]. In 1990, among the states participating in the Behavioral Risk Factor Surveillance System, 10 states had a prevalence of obesity less than 10% and no states had prevalence equal to or greater than 15%. In comparison, in 2009, only nineteen years later, only Colorado and the District of Columbia had a prevalence of obesity less than 20%. Thirty-three states had a prevalence equal to or greater than 25%; nine of these states had a prevalence of obesity equal to or greater than 30%[306]. While the prevalence of obesity varies by age and sex, and by race-ethnic groups[306,307], in 2007-2008 the overall rate of obesity in the U.S. was 32.2% among adult men and 35.5% among adult women. Despite this alarming trend, Flegal *et al.*[305] recently reported that in women and possibly in men, the increases in the prevalence of obesity did not appear to be rising at the same rate over the past 10 years and it had in years prior.

1.2 Obesity is a Major Public Health Concern

A higher body weight is associated with increased incidence of a number of conditions, including diabetes mellitus, kidney disease, cardiovascular disease, nonalcoholic fatty liver disease, an increased risk of disability and deceased health-related quality of life[308–311]. The report *Healthy People 2010*[312] identified the condition of being overweight or greater as one of the ten leading indicators for health, and chronic obesity at middle age significantly increases lifetime Medicare costs relative to those who remain at normal weight[313]. Thus, the current proportion of obese people in the U.S. is alarmingly high and rates continue to rise. Furthermore, obesity increases disability and morbidity from a variety of other conditions and has important social and healthcare costs.

1.3 Obesity is Multifactorial and Related to Sleep

The etiology of obesity is believed to comprise genetic, metabolic, environmental, behavioral, and sociodemographic factors[314]. The recent rise in obesity suggests behavioral and environmental changes are the cause of the current epidemic[315,316]. In an analysis conducted by Chaput *et al.*[317], nine risk factors for obesity were evaluated from a six-year period of data collection. They found that sleep duration and eating behavior (i.e., high disinhibition and restraint eating) significantly predicted weight gain while, perhaps surprisingly, energy intake and physical activity did not.

The association between chronic sleep restriction and obesity is likely to be bidirectional and circular as symptoms of obesity such as pain and discomfort and comorbid conditions such as obstructive sleep apnea have been shown to impair and disrupt sleep[318]. Indeed, it has been reported that approximately 50% of obese people complain about the quality of their sleep[319]. While there are many factors proposed to contribute to energy imbalance in humans, evidence suggests that in those with weight pathology, even moderate weight loss (~-10%) can be beneficial in reducing levels of many co-morbid risk factors[320]. Given the alarming increase and significant burden of obesity, the identification and quantification of salient factors that either promote or decrease energy imbalance is of critical importance.

1.4 Sleep Times Are Reduced

Over the past 40 years, self-reported sleep duration in the U.S. has decreased by almost 2 hours[52,321–324]. In 1982, a study from the American Cancer Society queried 1.12 million Americans and found that average sleep duration per night was distributed approximately normally (e.g., 52.4% = <7.5h; 19.7% = <6.5h; 4.0% = <5.5h)[325]. In contrast to this study, a 2005 Gallup poll found that among 1,500 U.S. adults, the average self-reported sleep duration was 6.8 h on weekdays and 7.4 h on weekends[326]. In corroboration of this finding, a U.S.-based survey conducted by the National Sleep Foundation in 2009 found that, compared to 2001, the amount of Americans that report average sleep time of less than 6 h per night has significantly increased (from 13% to 20%), while the amount who report 8 h or more has significantly decreased (from 38% to 28%)[327]. It is likely that a multitude of factors contribute to chronic sleep restriction, including chronic physical and mental health status (including sleep disorders), environment, sociodemographic status, and lifestyle[318,328]. Additionally, in America, both work and commute times are extending, which may encourage Americans to voluntarily curtail sleep duration in order to have more available wake time for non-work activities[52].

2. Sleep Times Impact Body Weight

2.1 Reduced Sleep, Weight, and Energy Regulations

2.1.1 *Epidemiological Evidence*

Reduced average sleep times could be critical to the rising rates of obesity as sleep duration has been shown to be closely associated with body weight[324,325]. Large questionnaire-based, population samples have shown an either an inverse or curvilinear dose-response relationship between sleep duration and BMI in adults[324,325,329–340].

In a study by Watson *et al.*[341] from the University of Washington Twin Registry (average age 36.9 years; 69% female), the researchers used a multivariate adjusted analysis on data from 1,224 monozygotic (423), dizygotic (143), and indeterminant (46) pair samples to showed that, within twins, shorter sleepers (<7 h/n) had a higher BMI (25.8 kg/m^2) than the BMI (24.9 kg/m^2) of the twin who slept longer (7-

8.9 h/night; p = 0.02)[341]. This finding stresses that environmental factors such as sleeping behavior are likely important indicators for body weight.

Epidemiological evidence has also shown a similar effect in children. Persistently short sleep duration (<10 h) during early childhood significantly increases the risk of excess weight or obesity in childhood, and appears to be independent of other obesogenic factors[342–345], even when adjusting for physical maturation and socio-economic status[346]. Importantly, sleep curtailment during youth has been associated with future weight gain[333,346]. To test associations between daytime and nighttime sleep duration and subsequent obesity in children and adolescents, Bell *et al.*[347] used a prospective cohort from a Panel Survey of Income Dynamics Child Development supplements (1997 and 2002) from U.S. children, ages 0 to 13 years (n=1930). The authors found that insufficient nighttime sleep among infants and preschool-aged children may be a lasting risk factor for subsequent obesity and that napping does not appear to be a substitute for nighttime sleep in terms of obesity prevention.

To help further assess this field of study, systematic literature review and analyses have taken place. Nielsen *et al.*[348] performed a systematic literature review of 71 original studies investigating the association between short sleep and weight gain. Overall, they found short sleep duration to be consistently associated with the development of obesity in children and young adults, but not consistently so in older adults[348]. Cappuccio *et al.*[338] also performed a systematic literature review and identified 696 studies, of which 45 met the inclusion criteria (19 in children and 26 in adults) and 30 (12 and 18, respectively) were pooled in the meta-analysis for a total of 36 population samples. Together, this analysis assessed data from 634,511 global subjects (30,002 children and 604,509 adults) across all ages (2 to 102 yrs) and genders. The pooled odds ratio (OR) for short duration of sleep and obesity was 1.89 (p<0.0001) for children and 1.55 (p<0.0001) for adults. In adults, the pooled beta for short sleep duration was -0.35 unit change in BMI per hour of sleep change. In total, this analysis found that cross-sectional studies from around the world show a consistent increased risk of obesity amongst short sleepers in both children and adults[338].

2.1.2 *Actigraphy and PSG Evidence*

Several reports have shown that self-report sleep duration may not accurately assess actual sleep duration[345,349]. In addition to questionnaire-based reports, studies utilizing objective measures, such as actigraphy and PSG, have been performed to assess the sleep-weight relationship[323]. In the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study (2000–2006), researchers used several nights of wrist actigraphy to measure sleep among a cohort of 612 middle-aged subjects to examine whether average sleep duration is associated with BMI, and 5-year change in BMI. In their cross-sectional analysis, shorter sleep was strongly associated with higher BMI and the association was very strong in persons who reported snoring, but weak in those who did not. Importantly, there were no

longitudinal associations between sleep measurements and change in BMI over the 5-year assessment period[323,349,350].

In a study that assessed the connection between sleep duration and BMI in older adults (aged 67-99 years), Patel *et al.* used wrist actigraphy to evaluate 6097 older men and women. Adjusting for sleep apnea, insomnia and daytime sleepiness, the authors compared relatively short sleepers to those sleeping an average of 7-8 h per night. A sleep duration of less than 5 h was associated with higher average BMI and greater odds of obesity, for both men (BMI=2.5 kg/m^2 greater; obesity=3.7-fold greater) and women (BMI=1.8 kg/m^2 greater; obesity=2.3-fold greater), respectively. In addition, short sleep was also associated with central body fat distribution and increased percentage of body fat[350]. A similar study using wrist actigraphy in community-dwelling elderly population (mean age 68.4±6.9 years, range, 57-97) showed that sleep duration had a U-shaped relationship with BMI and obesity, such that higher BMI was seen in both short (<6 h) and long sleepers (≥8 h), compared to subjects who slept 7 to <8 h[349].

Studies utilizing PSG have also shown a similar relationship between sleep duration and BMI. A population-based longitudinal study with 1,024 volunteers from the Wisconsin Sleep Cohort also showed a U-shaped curvilinear relationship between sleep duration and BMI where the minimum BMI was predicted at an average of 7.7 h of sleep per night. The authors further commented that in persons sleeping less than 8 h, an increase in BMI was proportional to decreased sleep[324]. Another study utilizing PSG in a population of Swedish women showed an inverse relationship between short sleep duration and anthropometric measurement of central obesity, even after adjusting for confounders such as age and lifestyle parameters like exercise, smoking and alcohol consumption. Additionally, the duration of SWS and REM sleep were both inversely related to waist circumference suggesting that the loss of specific sleep stages may be important factors in the association between sleep loss and central obesity[351]. However, the results of this study are cross-sectional and do not allow any inference about causality.

Therefore, while inconsistent findings have been reported, there does appear to be a relationship between sleep duration and BMI. This relationship may not be monotonic but rather curvilinear, such that higher BMI associates with both shorter and longer sleep durations. However, the influence of absolute sleep duration and abnormal BMI may depend on age. For example, 10 h of sleep in adolescents appears to pose no sleep-related obesogenic risk, whereas, for adults and the elderly, that same absolute sleep duration appears to be associated with a greater risk for increased BMI. Thus, over the course of a lifespan, there may be increased risk for weight gain if a person is to get less or more sleep that what is considered average for their age.

2.2 Sleep Elongation, Weight, and Energy Regulation

One notable recent pediatric study showed for the first time that experimental sleep elongation reduced caloric intake. To our knowledge, this is the first time that

such an effect like has been shown. This work done by Hart *et al.*[352] used a within-subjects, counterbalanced, crossover design, with 37 children aged 8 to 11 years old in a three-week study. Participants achieved a 2 hour, 21-minute difference in the actigraph-defined sleep period time between the increase and decrease sleep conditions ($p < 0.001$). Compared with the decrease sleep condition, during the increase condition, children reported consuming an average of 134 kcal/day less ($p<0.05$) and exhibited lower fasting morning leptin values ($p<0.05$). However, it should also be noted that this study utilized food recall questionnaires, which is not an accurate way to measure actual food intake.

3. Potential Causes of Weight Gain with Sleep Disturbance

3.1 Metabolic, Endocrine, Immune, and Autonomic Relationships

Sleep plays an important role in neuroendocrine and metabolic functioning. There is abundant evidence from epidemiologic studies and well-controlled laboratory studies in both animals and humans that indicate that sleep curtailment and sleep disruption have adverse effects on metabolic parameters involved in energy regulation and, thus, body weight. The direction of these associations has not yet been confirmed, but it appears that the abnormal sleep patterns can increase the risk of weight gain. For instance, impaired sleep has been associated with alterations in appetite-regulating hormones and with glucose and adipose regulation, which indicate that fat accumulation may be promoted. Additionally, changes in energy expenditure, core body temperature, and circadian rhythms synchronization may also arise, promoting a condition for greater metabolic efficiency and increased risk of weight gain.

3.1.1 *Glucose Metabolism*

Reduced sleep and disrupted sleep have been associated with both metabolic abnormalities and metabolic disorders related to glucose regulation. Individuals who sleep either less than six hours or more than nine hours have been shown to have a higher incidence of diabetes mellitus and impaired glucose tolerance compared to those who sleep seven to either hours per night[353]. Epidemiological studies have shown an independent association between sleep-disordered breathing and both decreased insulin sensitivity[354] and incident diabetes[355,356].

Interventional, partial sleep restriction studies in humans have also shown a connection between reduced or disrupted sleep and impaired glucose tolerance and decreased insulin sensitivity in both healthy subjects[357] and in subjects with type 1 diabetes[358]. In 1997, Eve Van Cauter and colleagues[359] first documented aberrant glucose regulation after sleep restriction. The study compared a group getting 4 hours of time-in-bed to a group getting 12 hours of time-in-bed over the course of 6 days and found that the group with restricted time for sleep expressed a glucoregulatory pattern similar to pre-diabetes mellitus. Sleep-restricted patients had a 30% decrease in glucose effectiveness, decreased glucose tolerance, and a 40% slower rate of glucose clearance, but no significant differences in insulin

sensitivity. Further evidence of a detrimental effect of aberrant sleep on glucose control came from a study that evaluated 400 females aged 20-70 years with one full night of PSG and found obstructive sleep apnea to be independently associated with decreased insulin sensitivity, indicating that sleep quality is important in glucoregulatory dynamics[351].

Animal studies have also supported these findings. A study with rats assessed the effects of 1 or 8 days of experimental sleep disturbance on parameters of glucose homeostasis. It was found that both moderate and severe sleep disturbance produced hyperglycemia and decreased insulin levels during intravenous glucose tolerance tests[360].

Sleep Stage Suppression

Following up on these findings, several studies probed this relationship further by looking at whether suppression of certain sleep stages impacts glucose regulation. It has been observed that the initiation of SWS temporally associates with changes in physiological parameters that could affect glucose homeostasis, such as decreased brain glucose utilization, stimulation of GH release, inhibition of corticotropic activity, decreased sympathetic nervous system activity, and increased vagal tone. In a study by Tasali *et al.*[361], nine healthy young subjects underwent 3 consecutive nights of selective suppression of SWS by acoustic stimuli. SWS suppression resulted in marked decreases in insulin sensitivity without adequate compensatory increase in insulin release, leading to reduced glucose tolerance. Furthermore, the magnitude of the decrease in insulin sensitivity was strongly correlated with the magnitude of the reduction in SWS. Similarly, Hertzog and colleagues[362] reported that, after SWS suppression through acoustic stimulation, a morning oral glucose tolerance test showed a decrease of up to 20% in insulin sensitivity as determined by the Matsuda Index. However, selective suppression of REM sleep did not affect next-day glucose homeostasis.

Interestingly, biopsies from human adipose tissue taken after interventional sleep restriction have been shown to exhibit insulin resistance[363,364].

Sleep, Appetite and Glucose Control

These findings provide strong evidence that glucose homeostasis is sensitive to changes in sleep duration and quality. Over time, altered glucose regulation may contribute to diabetes and weight gain. According to the Glucostatic Theory of Appetite Control, glucose plays an important role in the regulation of satiety and appetite[365,366], whereby low brain glucose utilization leads to the perception of hunger, whereas higher glucose utilization in these same areas promotes satiation[366]. In support of this theory, lower blood glucose concentrations at the end of an oral glucose tolerance test predicted weight gain over a 6-year period[367]. Additionally, impaired insulin sensitivity is one of the major defects underlying the development of type 2 diabetes, which is a disorder closely related in its occurrence to the occurrence of obesity. Thus, it is possible that chronic sleep

restriction contributes to obesity by disrupting the regulation of glucose in a manner that promotes increased food intake.

3.1.2 *Fatty Acid Metabolism*

While more research has look at sleep loss on sugar metabolism, there is research indicating sleep loss has a negative impact on fatty acid metabolism, as well.

The enzyme stearoyl-CoA desaturase 1 (SDC1) plays an important role in lipid biosynthesis and in regulating mitochondrial fatty acid oxidation. The expression of this enzyme may meaningfully influence the composition of fatty acids in lipid pools. One night of TSD has been shown to elevate levels of hepatic SCD1 expression and de-novo fatty acid synthesis. These changes were associated with increased DNA methylation at key sites regulating SCD1 expression, and therefore, at least some of the negative effects of sleep loss on fatty acid pools are thought to be epigenetically driven[368].

3.1.3 *Hormones*

3.1.3.1 *Cortisol and Glucagon*

The changes observed between reduced or disrupted sleep and impaired glucose tolerance may at least be partially explained by observed changes in glucoregulatory hormones. Activation of both the hypothalamic–pituitary–adrenal (HPA) axis and hypocretin neurons have been observed during sleep deprivation and sleep restriction and severe sleep restriction results in elevated evening cortisol levels[369] The deprivation of REM sleep appears to activate the HPA axis via increased levels of corticotropic-releasing hormone, adrenocorticotropic hormone and corticosterone[370]. Importantly, elevated cortisol levels have been shown to promote increased food intake and the accumulation of visceral fat in humans[371,372]. Reduced sleep also associates with reduced circulating glucagon levels[373].

Relative to the well-rested condition, Guyon and colleagues observed that after sleep loss the response to CRH from ACTH decreased by 27% and the response from cortisol decreased by 21%. In this study, the cortisol response showed reduced reactivity and slower recovery to the CRH indicating decreased adrenal sensitivity after sleep loss[374].

3.1.3.2 *Leptin and Ghrelin*

Leptin is another peptide hormone involved in energy homeostasis, the dominant role of which is to signal energy deficiency to the brain[375]. It is an adipokine produced primarily by subcutaneous white adipose tissue and its expression is stimulated by various hormones, sympathetic outflow, energy intake and output[375,376]. Under normal conditions, blood levels display circadian variation as

levels rise across the day and peak in the middle of the night[377]. During sleep deprivation, blood leptin levels show a reduced and flattened profile[378].

Ghrelin is a peptide hormone mainly produced by endocrine cells in the stomach and gastrointestinal tract, and is an important endogenous regulator of energy balance and GH secretion[201]. Its expression is complex[379] and influenced by sympathetic nervous system activity[380]. Across the wake period, plasma concentration wax and wane episodically providing an orexigenic signal to the brain[381]. During sleep, ghrelin levels increase in the early part of the night and decrease towards morning, however, this nocturnal increase is blunted during sleep deprivation[382].

Leptin, Ghrelin and Sleep

The association between leptin, ghrelin and sleep has been assessed in multiple studies. In a population-based study that evaluated 1,024 volunteers from the Wisconsin Sleep Cohort, morning fasted blood samples were analyzed for serum levels of leptin and ghrelin. Compared to individuals with a habitual sleep time of 8 hours, those sleeping only 5 hours were predicted to have 15.5% lower leptin and 14.9% higher ghrelin, independently of BMI This finding suggested that, regardless of BMI, short sleep duration may alter appetite regulating hormones in a way that can potentially increase the risk for weight gain[324].

Acute interventional studies have also shown a connection between sleep reduction and appetite regulating hormones. In the first study to report this connection in humans, Mullington *et al*.[383], evaluated leptin levels in response to 88 h of total sleep deprivation in 10 healthy men. They found evidence that sleep influenced the nocturnal leptin profile such that the diurnal amplitude of leptin was reduced during sleep deprivation and returned toward normal during the period of recovery sleep. A subsequent study by Spiegel *et al.*[321] evaluated 12 healthy young men with normal BMI under conditions of less severe sleep restriction. In this randomized, crossover clinical study, subjects underwent 2 days of both sleep restriction (4 h time in bed) and sleep elongation (10 h time in bed) while being controlled for caloric intake and physical activity. Similar to Mullington's total sleep deprivation study, sleep restriction also associated with a significant decrease in leptin (-18%; $p=0.04$). This study also showed a significant increase in ghrelin (+28%; $p<0.04$), hunger (+24%; $p<0.01$) and appetite (+23%; $p=0.01$), especially for foods of high caloric-density with high carbohydrate content (+33% to 45%; $p=0.02$).

The reduction of leptin levels seen with acute sleep restriction have been associated with elevated sympathovagal balance, and altered cortisol and thyroid stimulating hormone profiles[376]. Additionally, in overweight individuals undergoing controlled, reduced calorie consumption, 14 days of interventional sleep restriction to 5.5 hours/night also appeared to promote perturbations in appetite regulating hormones, such that body weight adjusted 24-hour ghrelin concentrations, and the ratio of ghrelin to leptin in the circulation, were significantly increased[384].

Of note, several studies failed to show a connection between sleep reduction and changes in leptin and ghrelin levels. These studies cite increased activation of the hypocretin system to account for changes induced by sleep deprivation, especially hyperphagia[369]. Other studies have also noted a decrease in daytime physical activity as the potentially important behavioral mechanism for the health-impairing influence of sleep loss[385].

3.1.4 Endocannabinoids

Endocannabinoid System and Feeding

The endocannabinoid system is a key component of pathways involved in modulating appetite, food intake, and energy homeostasis. The endocannabinoid receptor, CB1, is found in hypothalamic nuclei involved in energy homeostasis and in the mesolimbic system, including the nucleus accumbens and ventral tegmental area[386,387]. Activation of CB1 receptors promotes hunger, whereas CB1 agonists suppress appetite[388,389]. In particular, endocannabinoid binding to CB1 receptors on dopamine and opioid pathways evoke a preference for highly palatable rewarding food[389–391].

Endocannabinoids and Sleep

In regard to energy regulation, there's notable overlap between the effects of activation of the endocannabinoid system and the effect of disrupted sleep. Similar to what is observed with sleep loss, increased activity of the CB1 receptor promotes feeding behavior in excess of energy need, reduces glucose tolerance, tends to reduce leptin levels and to promote ghrelin release, and stimulates reward centers. It has been shown that decreased sleep enhances the daily rhythm of the endocannabinoid 2-Arachidonoylglycerol (2-AG)[392], which naturally leads to the hypothesis that altered endocannabinoid activity during sleep restriction mediates sleep loss-induced changes in energy homeostasis.

To explore this, Hanlon and colleagues[392] conducted a randomized crossover study comparing 4 days of bedtime restriction to 4.5 hours per night to regular 8.5-hour bedtimes in non-obese healthy individuals. In the sleep debt condition, these researchers found that the amplitude of the daily rhythm of circulating concentrations of 2-AG was amplified due to higher and extended peak afternoon concentrations, without change in the level or timing of the nocturnal nadir. This suggested that the early afternoon drive for hedonic eating may be stronger and last longer in a state of sleep debt. Concurrent with the altered endocannabinoid levels, sleep restricted participants, despite reporting fullness after a normal-sized meal, reported higher scores for hunger, desire to eat, quantity of food that could be eaten, and appetite. The authors hypothesized that these increases in peripheral endocannabinoid concentrations could be a mechanism by which recurrent sleep restriction results in excessive food intake, particularly in the form of snacks, despite minimal increases in energy need.

3.1.5 *Immune system*

Shorter sleep duration and certain sleep disorders like insomnia and sleep apnea are associated with increased markers of inflammation, including C-reactive protein (CRP) and interleukin-6 (IL-6). Epidemiological evidence shows that poor sleep associates with elevated inflammation[393]. Studies have also shown that a full night or partial night sleep deprivation leads to next day activation of inflammatory signaling pathways[394,395]. Importantly, systemic inflammation is associated with insulin resistance and with effectors of the adipostat[396]. Furthermore, inflammatory signals have been shown to be soporific, as IL-6 can promote sleepiness. It is plausible that sleepiness can have an effect on activity levels, which may further affect sleep and metabolic sensitivity to energy substrates and hormones. Observational studies have shown that shift workers have increases in circulating levels of inflammatory markers[397], as do older adults, who have poorer sleep than younger adults[398].

3.1.6 *Energy Expenditure and Temperature*

Energy Expenditure

It is well known that individuals vary considerably in terms of rate of energy expenditure, even when corrected for differences in fat free mass. Total daily energy expenditure is primarily comprised of activities that take place during waking, such as one's basal metabolic rate which results from such things as homeothermy and maintenance cellular functions, and activity-and-diet induced thermogenesis. Additionally, sleep metabolic rate is estimated to comprise roughly 25% of total daily energy expenditure[399]. Interestingly, sleep reduction has been shown to influence next day energy expenditure in inconsistent ways. In rats, sleep deprivation between 24 to 96 h and sleep restricted for 21 days rapidly increased energy expenditure and led to a negative energy balance. These changes in energy expenditure were mostly attributed to activation of the hypocretin system[369].

The prolonged suppression of REM sleep has been associated with increased activation of the HPA axis, and with loss of body weight despite an increase of food intake. This apparent paradox between loss of body weight and increased energy consumption could be a result of an increase in energy expenditure. In 2009, Galvao *et al*.[370] examined the mechanism involved in the influence of REM sleep deprivation on metabolism, feeding behavior and stress response. REM sleep depression resulted in increased diurnal food intake, however, produced no significant changes in food intake over a 24-hour period.

In human studies, compared to baseline standards, sleep restriction has produced highly inconsistent results related to alterations in daytime physical activity and resting metabolic rates[384,385,400].

Temperature

Core body temperature may also be an important factor influencing energy expenditure and, therefore, energy balance. It is known that a decrease in body temperature occurs at night in relation to the sleep cycle in human populations[401]. It has also been hypothesized that lower body temperatures may contribute to decreased energy expenditure of the obese state[402,403]. However, a study that restricted sleep over a 14-day period found no significant decrease in core body temperature from sleep restriction[404]. Further research is necessary to know if chronic sleep reduction is accompanied by a reduction in core body temperature that would promote greater metabolic efficiency and increase risk of weight gain.

3.2 Chronobiology

3.2.1 *Circadian Introduction*

Nearly every physiological and biochemical function of the body shows rhythmic circadian variations. These circadian rhythms are biological events that constantly repeat in a 24-hour period and are generated by endogenous mechanisms, or clocks, that allow the organism to predictively adapt to changes in its environment[405]. The optimization of the organism's time-of-day responses depends on both the synchronization between external environmental cycles and signals with the clock system intrinsic to the organism, and the synchronization of central (superchiasmatic nucleus) and peripheral (local, tissue specific) clocks within the organism.

3.2.2 *Circadian Metabolism*

Energy homeostasis is impacted by cellular and behavioral chronobiology. The adipocyte generates patterns of signals across the 24-hour period that influence satiety, cellular differentiation and proliferation. Behaviorally, time of day influences food intake patterns, and, conversely, food intake timing, frequency, regularity and composition may affect chronobiological patterns of both the central clock and peripheral clocks, as in adipose tissue[406]. Chronic desynchronization of the circadian system may promote energy efficiency, and thus, obesity[407]. Work from the Turek lab has evaluated the role of the circadian phase of food consumption and how food consumption influences the mammalian clock. For example, in one study, mice fed a high-fat diet only during the 12-hour light phase gained significantly more weight than mice fed only during the 12-hour dark phase[408]. In separate studies, they demonstrated how the consumption of a high-calorie diet alters the function of the mammalian circadian clock[409] and that the circadian clock gene network plays an important role in mammalian energy balance both at the behavioral and molecular level[410].

Shift workers have a chronic desynchronization of endogenous rhythms due to frequent alterations in the sleep/wake pattern. Shift work is associated with a variety of metabolic disturbances, including decreased HDL cholesterol and increases in fasting glucose, triglycerides, free fatty acids, arterial blood pressure,

abdominal circumference, and BMI[411,412]. Shift work has also been associated with greater incidence of cardiovascular disease, diabetes, and obesity[413]. This chronic desynchronization of endogenous rhythms may also alter eating behaviors and it has been shown that shift workers eat more meals during the evening and night[412]. Thus, it appears probable that circadian desynchronization and other behaviors such as eating timing can alter clock genes and rhythms and can interfere with the complex mechanism of metabolic and hormonal patterns, contributing to diseases such as energy imbalance (i.e., obesity) and energy-system dysregulation (i.e., diabetes)[406].

3.3 Altered Energy Intake and Expenditure

3.3.1 *Energy Intake*

Appetite and hunger

Sleep restriction has been shown to increase appetite and the preference for meals that contain high carbohydrate content[321]. In one study, ten young lean healthy subjects were presented with an assortment of *ad lib* food tailored to meet their dietary preferences, including a buffet lunch and dinner and unrestricted access to snacks, after 4 consecutive nights of 4.5 hours in bed. Compared to an 8.5-hour sleep baseline condition, sleep restriction associated with a ~15% increase in total caloric intake and ~10% increase in carbohydrate intake[414]. In another study, when compared to a group of control subjects who received 8 hours of sleep, after one night of sleep restriction to 4 hours, subjects consumed 22% ($p<0.01$) more energy and had greater preprandial hunger before breakfast ($p<0.001$) and dinner ($p<0.05$) without a change in the perceived pleasantness of the foods or in the subjective desire to eat the foods. Interestingly, despite being significantly more sleepy, the sleep restriction group was also significantly more physically active between the hours of 12:15 and 20:15[400].

Calorie intake

Previous research showed that insufficient sleep leads to increased calorie intake. Work by Calvin *et al.*[415] comparing the caloric intake in conditions of usual sleep versus a sleep restriction of two-thirds of normal sleep time, for 8 days/8 nights, in a hospital-based clinical research unit. Caloric intake in the sleep-restricted group increased by +559 kcal/day ($p=0.006$) and decreased in the control group by −118 kcal/day ($p=0.51$) for a net change of +677 kcal/day ($p=0.0149$).

Snacking

Research by Spaeth *et al.*[416] and Markwald *et al.*[417] supports indicated that chronically sleep-restricted adults with late bedtimes seem more susceptible to weight gain due to greater daily caloric intake, and that much of this surplus may take place in the hours immediately prior to bedtime, when sleep deprived people consume highly palatable, calorically-dense foods.

In the largest, most diverse healthy sample studied to date under controlled laboratory conditions, Spaeth *et al.*[416] assessed body weight at admittance and discharge in 225 subjects, and evaluated the time-course caloric intake and meal timing following 2 baseline nights, 5 nights of sleep restriction (4 h time in bed) and 2 recovery nights, or following control conditions (10 h time in bed/night). Compared to control subjects, sleep-restricted subjects gained more weight than control subjects ($p=0.007$) and consumed extra calories ($p=0.003$). The increased daily caloric intake was due to more meals and the consumption of 552.9 ± 265.8 additional calories between 22:00-03:59. The percentage of calories derived from fat was greater during late-night hours compared to daytime and evening hours ($p< 0.05$).

In other research, Hogenkamp *et al.*[418] used a randomized within-subject design (n=16) to compare portion size choice after a night of 8 hours sleep and a night of sleep loss. In the morning after sleep loss, subjects had increased plasma ghrelin levels (13%, $p=0.04$), increased self-reported hunger ($p<0.01$), and chose larger portions (14%, $p=0.02$), irrespective of the type of food, as compared to the sleep condition. Additionally, following breakfast, sleep-deprived subjects chose larger portions of snacks (16%, $p=0.02$), yet meal items did not differ between interventions. The researchers concluded that after sleep loss, overeating in the morning is driven by both homeostatic and hedonic factors, and that portion size choice after sleep loss depends on both an individual's hunger status, and the type of food offered. In a separate paper from the same study[419], this research group reported on food purchasing behaviors after sleep deprivation. They found that independently of both type of food offered and food price, sleep-deprived men purchased significantly more calories (+9%) and grams (+18%) of food than they did after one night of sleep (both $p<0.05$).

It must be considered that sleep reduction may increase food intake, not only by alterations in homeostatic mechanisms that control hunger, but also due to the increased time of exposure to food. Also, sleep loss may affect decision making processes involved in food choices and eating behaviors.

3.3.2 *Energy Expenditure*

In contrast, other studies have shown that acute sleep restriction did not increase food intake but decreased next-day physical activity. In one study[385], the authors postulated that the observed decrease in daytime physical activity could be a salient behavioral mechanism for the health-impairing influence of sleep loss.

Many studies have shown that alterations in energy regulating hormones, like leptin and ghrelin, correlate with sleep deprivation. However, these changes may not represent a unique effect of sleep deprivation on their metabolism. Alterations in the levels of these hormones would be expected due to increases in energy expenditure, which take place as a consequence of the additional hours of wakefulness, by opposition to the reduced metabolic rate of the sleep state. A report by Markwald *et al.*[417] showed that after 5 days of sleep restriction (5 hours

of time in bed), insufficient sleep increased total daily energy expenditure by ~5% when compared to a 9-hour time in bed control condition. The increase in energy expenditure corresponded with increased food intake, which the authors noted is a normal physiological adaptation to provide the energy needed to sustain additional wakefulness. However, especially in women, insufficient sleep reduced dietary restrain, and energy intake was in excess of energy needed to maintain energy balance, especially at night after dinner. Interestingly, they also found that when subjects transitioned from an insufficient to adequate/recovery sleep schedule, energy intake—especially of fats and carbohydrates—decreased and led to weight loss (−0.03 ± 0.50 kg).

3.3.3 Altered Energy Regulation Under Calorie Restriction

It has also been demonstrated that sleep restriction interferes with the beneficial effects of a reduced-calorie diet on excess body weight and adiposity. In one such study, overweight individuals underwent caloric restriction to 90% of their resting metabolic rate for a two-week period, while under two different sleep conditions, separated three months apart. While weight loss during each treatment remained similar, the composition of the weight loss differed markedly. In the 8.5-hour bedtime condition, fat constituted 57% of the lost weight. However, in the sleep restricted condition (5.5-hour bedtime), fat constituted only 26% of the weight loss and showed increased weight loss from lean body mass[384]. Together, these results show that sleep restriction may increase food intake, craving for carbohydrates, either increase or decrease physical activity, and reduce the beneficial effects of a reduced-calorie diet in those with excess adiposity.

4. Sleep, Brain Processing, and Energy Regulation

4.1 Arousal, Attention, Cognition, Affective Processing, and Sleep

4.1.1 Vigilance Regulation

In the two process model for sleep and wake offered by Borbely *et al.*[420], vigilance is affected by two, mutually exclusive processes that combine to influence the human sleep-wake cycle: 1) a homeostatic process that builds up pressure for sleep during wakefulness and dissipates this pressure during sleep and 2) a wake-and sleep promoting circadian rhythm that oscillates in intensity over a 24-hour period[421].

Sleep can be reduced in a variety of ways, including partial or total sleep loss over a period of time. Sleep can also be reduced through fragmentation, which disrupts sleep architecture and can limit the actual amount of sleep achieved during a period of time in bed. In addition, selectively, a sleep stage can be reduced or eliminated while total sleep time remains intact. Voluntary sleep curtailment is a type of partial sleep deprivation in which individuals voluntarily reduce the amount of sleep they get on a chronic basis[422].

When sleep is reduced, vigilance performance deteriorates progressively over days and is dependent on total sleep lost during the observation period. Remarkably, 14 consecutive days of sleep restriction to 4-6 hours sleep periods impair behavioral alertness to the same degree as seen after 1-3 nights of total sleep deprivation, suggesting that the effects of sleep restriction accumulate over time[423,424]. As with vigilance performance, cumulative neurobehavioral deficits are also seen in other cognitive functions, including impairments in executive functioning, decision making, working memory, and emotional states[425–443]. In studies of total sleep deprivation, there is a monotonic relationship between deficits in neurocognitive performance and subjective ratings of sleepiness. Interestingly, the accumulation of objective cognitive performance deficits seen with nightly sleep restriction below 8 hours is not paralleled by equivalent subjective ratings of sleepiness[424,444]. This mismatch between subjective perception of sleepiness and actual cognitive impairment may lead people to underestimate the actual degree to which they are cognitively impaired and overestimate their readiness to perform tasks[445]. Notably, there are also considerable individual differences in the degree of vulnerability to performance impairment from sleep loss, and these differences represent a trait[425,446–450].

Vigilance performance decrements in response to sleep loss also show a time-of-day effect such that, during periods of sleep restriction, significant differences in vigilance performance and subjective sleepiness[451] will be seen at various time-points across a 24-hour period. Compared to diurnal periods, worse performance tends to take place during habitually entrained night periods[421]; however, additional variation takes place within diurnal and nocturnal time frames. For example, Mollicone *et al.* showed that following 8 days of sleep restriction to 4 hours/day, diurnal vigilance errors were worst at 08:00 and became progressively smaller across the hours of the day, especially between 16:00 and 20:00[451]. Remarkably, subjects averaged 8.3 more Psychomotor Vigilance Task performance lapses at 08:00 than at 18:00[451]. It has been suggested that circadian wake processes facilitate a period of relatively protected alertness in the late afternoon and early evening hours when nocturnal sleep is chronically restricted[451].

4.1.2 *Compensatory Sleep*

A compensatory mechanism to support vigilance performance appears to exist to withstand acute reductions in sleep. As homeostatic pressure for sleep builds up higher across prolonged wakefulness, the rate of dissipation of that pressure during subsequent sleep is enhanced exponentially, so that even brief periods of sleep provide significant performance recuperation[421]. Depending on the timing and duration of sleep, and the number of days it is reduced relative to normal, average sufficient sleep of 8 hours per night, some aspects of sleep are conserved, occur sooner, or intensify, while other aspects of sleep are diminished[423,424,452,453]. Banks *et al.*[454] showed that after 5 nights of sleep restriction to 4 h per night, sleep parameters such as total sleep time, stage 2, REM sleep and NREM slow wave energy, and the objective Maintenance of Wakefulness Test, increase monotonically across an ascending dose of sleep recovery time that ranged from 4

to 10 hours. However, other neurobehavioral deficits induced by sleep restriction, such as decrements in vigilance and subjective sleepiness (as measured by the Psychomotor Vigilance Task and Karolinska Sleep Scale, respectively), improved exponentially after recovery sleep. It is important to note that one night of sleep recovery up to 10 hours of time in bed was insufficient to abolish all vigilance, subjective sleepiness and mood deficits caused by the 5 nights of sleep reduction in this experiment[454]. The authors concluded that complete recovery from such sleep restriction may require a longer sleep period during one night, and/or multiple nights of recovery sleep[454].

4.1.3 *Executive Functioning*

4.1.3.1 *Introduction*

Sleep deprivation adversely affects the ability to perform cognitive tasks. However, it is uncertain if sleep deprivation selectively reduces the capacity of specific cognitive functions, such as the executive functions, or if the observed cognitive decline is the result of a global cognitive impairment due to reduced stability in attentional networks[455].

An executive act is any act toward oneself intended to influence future outcomes via self-regulated behavior and is therefore instrumental to purposive, intentional behavior[456]. The executive functions are thought to be processes that allow for the development of a temporally remote goal and the ability to work towards that goal. This requires retaining the goal in memory, maintaining attention to the goal to inhibit distractions and competing responses, and modifying original plans to meet expected outcomes[457]. Together, these cognitive abilities are thought to be instrumental in the execution of complex tasks such as interpersonal communication, creative problem solving, and decision making[458]. It has been hypothesized that these abilities may have developed as an adaptation to environmental pressure associated with group and social living[456]. It is also believed that the executive functions strengthen from birth to adulthood as demonstrated by the remarkable shift over the first three decades of life toward a greater performance on functions such as delaying gratification versus selecting an immediate reward but at a cost for its immediacy[459]. Furthermore, executive functions have been shown to be distinct from other cognitive functions, like intelligence[460].

Component cognitive functions that comprise the executive function abilities include attention and concentration, memory (working and verbal), behavioral flexibility, planning, and response inhibition. Additionally, it has been hypothesized that emotional responses—triggered by environmental cues—provide initiative and energizing behavior for goal attainment and therefore influence the decision making process in an adaptive manner[461]. Brain areas relevant to these related functions include specific parts of the cortex (i.e., the anterior cingulated, dorsolateral prefrontal, and orbital frontal) and hippocampus[462], with the addition of limbic nuclei and the inferior medial frontal region of the cortex (anterior cingulated) for emotional processing[461]. To assess aspects of brain activity related

to various cognitive demands, Duncan *et al.*[463] reviewed functional neuroimaging patterns of frontal-lobe activation, including aspects of perception, response selection, executive control, working memory, episodic memory, and problem solving. They found strong evidence for regional specialization of function within prefrontal cortex indicating same brain regions may subserve different functions in different behaviors. However, this specialization poses a methodological problem for studying distinct components since a specific frontal-lobe network is consistently recruited for diverse cognitive problems[463].

4.1.3.2 Sleep and Executive Functioning

It has been hypothesized that sleep restriction directly impairs executive functions and performance on tasks that rely on prefrontal cortical function more than non-executive task performance[464]. This stems from various findings that show total sleep deprivation selectively alters theta power density[16, 17] in the frontal cortex and metabolism in the prefrontal cortex[428] during wake periods. While research on the effect of sleep restriction on executive function has been studied extensively[436,443,464–477], a clear association has been hard to discern due to inconsistent findings and task impurity problems[473,475,476,478]. One study that did find an association between sleep reduction and executive impairment assigned 106 new parents to either a sleep-curtailed group (<7 hours/night) and a non-sleep-curtailed group (≥7 hours/night) based on self-reported nighttime sleep duration from a 6-month period immediately preceding the study. In this study, the ability to flexibly implement a task goal was significantly impaired in the sleep curtailed group[479]. Contrary to this finding, Tucker *et al.* studied the effects of sleep deprivation on executive functions using a task battery that allowed dissociation of some important executive processes from non-executive components of cognition. While performance on the control task battery was considerably degraded during sleep deprivation[477], working memory scanning efficiency, resistance to proactive interference, and dissociated executive processes of phonemic verbal fluency performance were not significantly impaired compared to baseline. These results challenge the view that executive functions are especially vulnerable to sleep loss[477].

Alternatively, Dinges and colleagues hypothesized that sleep-deprivation induced cognitive impairments result from instability in the wake state[449]. Similar to the two process sleep wake model from Borbely *et al.*[420], the homeostatic drive for sleep and the circadian drive for wakefulness—with the addition of a compensatory effort to perform— interact to determine the net state of vigilance and cognitive performance. Furthermore, during conditions of sleep loss, there is an increase in moment-to-moment variability of attention which then impairs a wide variety of cognitive tasks, including executive functions that are necessary for goal-directed activities[449]. Thus, according to this model, sleep deprivation does not necessarily cause selective impairments in executive functions due to discriminant prefrontal cortex vulnerability to sleep loss. Rather, sleep deprivation affects cognitive performance globally, at least in part, due to deficits in the ability to sustain attention.

While sleep deprivation may not affect the executive functions more than other cognitive functions, executive abilities may still be impacted in a vigilance-impaired condition. Due to the prefrontal cortex specialization for a variety of discrete behavioral abilities, various instruments used to assess executive functions are complicated by task impurity[480], as executive functions both operate on, and are operated on by other cognitive processes. Therefore, any task that targets executive functions also likely implicates non-executive cognitive processes. An impaired non-executive process serving as a weak link in the executive system may diminish the overall executive functions score; however, this low score would not necessarily arise from impairment of the target executive functions[481]. Even then, research on sleep restriction can assess functional loss of abilities related to executive function, but it is still difficult to claim that any observed effects would be a result of impairment primarily in executive systems and not the non-executive systems they influence or that influence them.

4.1.3.3 Behavioral Choice Theory and Delay Discounting

A theoretical approach to assess executive functioning is behavioral choice theory, or behavioral economics. This paradigm combines research from a variety of disciplines to help understand how people make decisions and has been extended to health behaviors, such as eating, physical activity, and obesity[482]. Choice research uses various models to assess choice decisions across concurrent alternative reinforcers or choice alternatives that vary temporally[483]. As an example of the second model of choice, the Delay Discounting paradigm assesses the degree to which a commodity fluctuates in reward value as a function of time. The measurement assesses the willingness to postpone receiving an immediate reward in order to gain additional benefits after a time delay for acquisition. Delay discounting is thought to assesses a variety of hallmark executive functions such as risk/benefit calculation, inhibitory control, and delayed gratification[456,484].

Delay discounting scores have been shown to predict the likelihood to engage in what are thought to be a range of health-related behaviors. For example, steep time discounting decreases the probability of engagement in anti-obesogenic behavioral habits, such as regular exercise and healthful eating patterns[485,486] and predicts higher energy intake in food reinforcement paradigms[483]. An analysis performed by Ikeda *et al.* on data from 2,987 respondents (average age = 49 years; 47% male) from the Japan Household Survey on Consumer Preferences and Satisfaction 2005 (JH05) show that obesity results in part from temporal decision biases[487]. Future reward discounting was positively associated with BMI, impatience, and inclination toward procrastination. A one-unit increase in the degree of procrastination was associated with a 2.81 percentage-point increase in the probability of being obese. Alternatively, respondents exhibiting the sign effect—where future negative payoffs are discounted at a lower rate than future positive payoffs (less risky)—show a 3.69 percentage-point lower probability of being obese[487]. In another study, obese and healthy-weight age-matched subjects completed Delay Discounting tasks assessing various monetary rewards over various time scales. Compared to controls, greater delay discounting was seen in obese women ($p<0.02$) but not in obese men. Subsequent analyses showed that

these differences between obese women and healthy-weight age-matched controls were not related to differences in IQ or income[488] Thus, differences in a person's preference for the present over the future may substantially influence their propensity to adopt a healthy lifestyle and affect weight gain.

4.1.3.4 Risk Taking and Working Memory

The reduced ability to delay gratification for a future positive outcome can be thought of as a form of impulsivity and risk-taking behavior. To study how sleep deprivation affects risk decisions with a potential loss-bearing outcome, Venkatreman *et al.*[476] deprived subjects of sleep for 24 h and then had subjects perform a gambling task while undergoing neuroimaging. Interestingly, they found that sleep deprivation modulated activation of various brain regions associated with risky decision making and emotional processing. For example, following sleep deprivation, riskier choices on the gambling task concurrently invoked a neural response indicative of elevated expectation for a higher reward and a diminished loss aversion. Neuroanatomically, this was represented by greater activation in the right nucleus accumbens and reduced insular and orbitofrontal cortices, respectively[476].

4.2 Sleep Disturbance, Brain Processing, and Energy Regulation

It has been reported that we make nearly 200 decisions per day about food[489]. Additionally, our awareness of a multitude of environmental factors can significantly influence what we eat and how much we eat. It has also been shown that certain environmental factors can lead to a misperception in the amount of actual energy consumed at a meal. For example, in *ad libitum* food environments, people eat different amounts depending on their awareness of how much they have already eaten[490]. Indeed, the quantity of food consumed by subjects in experimental procedures has been shown to be influenced by such things as: the size of food packaging, plate size and shape, meal portion size[491,492], ambient lighting and noise/music element of the room[493], temperature of eating environment[494–496], the number of people and the behaviors of those people whom we eat with[497,498], the variety of food types available to us, and the proximity and visibility of the food types in our environment[499]. Many of these environmental parameters serve to either establish social norms[500–502], which suggest appropriate consumption quantity, or distract from an awareness of actual energy consumed and internal cues of satiety[490,503]. In fact, environmental influences on eating behaviors, like portion size[504,505], have been shown to have increased in parallel with the rise in the prevalence of obesity[506–509]. Thus, the act of self-monitoring both actual consumption volume and satiety in diverse environmental settings requires awareness to resist excessive caloric intake.

4.2.1 *Altered Inhibitory Control and Energy Regulation*

The susceptibility to overeat has also been shown to be a product of disinhibitory control over the action to stop eating. Studies have shown that high susceptibility to overeat combined with low restriction is associated with higher body weight[510–

[513]. For example, in a cross-sectional study using survey data in Danish women, risky eating, in part defined as a self-rating of inhibitory control to stop eating, showed that this type of behavior was a risk factor for obesity[514]. Furthermore, this study showed that those with a BMI of 25 or more had an increased risk of maladaptive eating behaviors, including reduced inhibitory control, by approximately 2.5 times. In a model of dietary restraint proposed by Polivy and Hermann[515], the authors suggest how dieting itself might lead to weight gain by reducing cognitive control over the physiological cues of hunger. Notably, hypoglycemia and sleep loss have both been implicated in decreased neurocognitive function; however, in one study, one night of total sleep deprivation deteriorated neurocognitive function but did not do so in a synergistic manner to aggravate the impairing influence of acute hypoglycemia[516].

4.2.2 Altered Memory and Energy Regulation

Additionally, what a person eats may also be influenced by their memory of what they had previously eaten in a day. In a study by Higgs *et al.*[517], unrestrained eaters were examined to see how much they would eat after being cued or not cued of a recent eating episode. While subjective ratings of hunger, fullness, and desire to eat did not vary as a function of cue type, subjects who were cued about a recent meal ate less than those who received no cue. This result suggests that memory of recent eating is an important cognitive factor influencing food intake.

4.2.3 Altered Mood and Energy Regulation

As discussed, emotions and mood are hypothesized to play a key role in the decision making process[461] and have also been shown to be affected by sleep loss[518]. With food, emotional states have also been shown to impact eating quantity. For example, a study by Turner *et al.*[519] showed that positive mood resulted in consuming significantly less calories in those with a controlled eating style. By contrast, among those who presented an uncontrolled eating style, positive mood enhancement led to greater calorie consumption[519]. In addition, the suppression of emotion has been shown to lead to increased food intake[520].

4.2.4 Altered Reward Processing and Energy Regulation

Work by St-Onge *et al.*[521] showed that, compared to controls, sleep-restricted subjects had greater neuronal activity in response to food stimuli and consumed an average of 296 kcal more per day when sleep deprived compared to when they were well rested. Similarly, Benedict *et al.*[522] found that acute sleep loss enhances hedonic stimulus processing in the brain, leading to an increased drive to consume food and coinciding with increased self-reported hunger. Other studies by St-Onge *et al.*[523] and Greer *et al.*[524] provided possible models of neuronal mechanisms that relate short sleep to altered appetitive drive increasing the risk for calorie surplus and the development of obesity. The St-Onge study[523] used fMRI in 25 normal weight subjects after a period of five nights of either 4 or 9 hours in bed to determine whether specific neural systems are preferentially activated after sleep

loss in response to unhealthy compared with healthy foods. After sleep restriction, viewing unhealthy foods led to greater activation in brain reward and food-sensitive centers such as the superior and middle temporal gyri, middle and superior frontal gyri, left inferior parietal lobule, orbitofrontal cortex, and right insula, compared with healthy foods. Further, food intake increased in association with a relative decreased activity observed in the right insula. The Greer *et al.* study[524] used a food-desire task in combination with fMRI to characterize the impact of sleep loss on the brain mechanisms governing appetitive food desire. Subjects (23 normal weight men and women) underwent a repeated-measures, counterbalanced, crossover-design trial involving a night of normal rested sleep (avg. 8h sleep) and a night of monitored total sleep deprivation (avg. 24h awake), separated by 7+ days. In this study, during food desirability choices after sleep deprivation there was decreased activity in appetitive evaluation regions within the human frontal cortex and insular cortex, and amplified activity within the amygdala. This brain activity pattern associated with a significant increase in the desire for high-calorie foods, the extent of which is predicted by the subjective severity of sleep loss across participants. The authors argued that this mechanism may explain how insufficient sleep leads to the development/maintenance of obesity through diminished activity in higher-order cortical evaluation regions, combined with excess subcortical limbic responsivity, resulting in the selection of foods most capable of triggering weight-gain. Together, these reports, and the previously reported work by St-Onge *et al.*[521] and Benedict *et al.*[522], illuminate a consistent association with short-term sleep loss and patterns of neuronal activity in brain centers involved in food reward and evaluation indicative of enhanced hedonic drive towards foods that are of high risk for maintaining a calorie surplus necessary for weight gain.

In the recent past, multiple important studies were reported evaluating calorie intake after insufficient sleep. While increased calorie intake would be expected after increased energy expenditure due to extended wakefulness, sleep deprivation may lead to a calorie intake that exceeds the expenditure differences between the sleep deprived vs. full sleep condition. While this surplus energy expenditure can occur from high calorie consumption at different parts of the day, there are several studies now that show the time immediately prior to sleep as particularly vulnerable for the consumption of high calorie meals that are comprised of calorie-dense foods. A potential mechanism that explains these observations is developed form imaging work that shows a pattern of neuronal activity after insufficient sleep in brain centers involved with food reward and evaluation. This pattern indicates that sleep loss enhances hedonic drive towards fattening foods. Together, these findings suggest that insufficient sleep does typically manifest in surplus energy intake and this surplus may be mediated by increased hedonic drive towards fattening foods, increased impulsivity, and increased willingness to eat foods that are believed by the subject to be unhealthy.