Regulation of Adolescent Sleep

Implications for Behavior

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ABSTRACT: Adolescent development is accompanied by profound changes in the timing and amounts of sleep and wakefulness. Many aspects of these changes result from altered psychosocial and life-style circumstances that accompany adolescence. The maturation of biological processes regulating sleep/wake systems, however, may be strongly related to the sleep timing and amount during adolescence—either as "compelling" or "permissive" factors. The two-process model of sleep regulation posits a fundamental sleep-wake homeostatic process (process S) working in concert with the circadian biological timing system (process C) as the primary intrinsic regulatory factors. How do these systems change during adolescence? We present data from adolescent participants examining EEG markers of sleep homeostasis to evaluate whether process S shows maturational changes permissive of altered sleep patterns across puberty. Our data indicate that certain aspects of the homeostatic system are unchanged from late childhood to young adulthood, while other features change in a manner that is permissive of later bedtimes in older adolescents. We also show alterations of the circadian timing system indicating a possible circadian substrate for later adolescent sleep timing. The circadian parameters we have assessed include phase, period, melatonin secretory pattern, light sensitivity, and phase relationships, all of which show evidence of changes during pubertal development with potential to alter sleep patterns substantially. However the changes are mediated—whether through process S, process C, or by a combination—many adolescents have too little sleep at the wrong circadian phase. This pattern is associated with increased risks for excessive sleepiness, difficulty with mood regulation, impaired academic performance, learning difficulties, school tardiness and absenteeism, and accidents and injuries.

KEYWORDS: circadian rhythms; sleep homeostasis; puberty; melatonin; adolescent humans; MSLT

INTRODUCTION

The timing of sleep and wakefulness undergoes one of the most prominent behavioral changes that occur during adolescent development, a change that occurs in a

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majority of young people. Data collected from many countries have confirmed the strong trend for later bedtimes and later rising times during the teen years, for example, USA,[1,2] Canada,[3] Switzerland,[4] Italy,[5] Taiwan,[6,7] Brazil,[8,9] and South Africa.[10] In each instance, the temporal delay of sleep timing manifests most clearly on non-school nights (weekends and vacations); even when the school schedule constrains rising times, the bedtime delay remains apparent on school nights.[11]

Explanations for this developmental pattern are easy to identify in the changing adolescent psychosocial milieu. Such processes as the growing expression of autonomy, the increase in academic obligations and social opportunities, as well as the rising availability of late evening activities offered by access to telephone, television, and Internet—all contribute in a significant way to the behavioral regulation of adolescent sleep patterns.

In addition, however, sleep and waking are under regulatory control by intrinsic brain mechanisms. The most well-known model describing these mechanisms was first expressed by Borbély as the "two-process model,"[12] a model subsequently refined by Borbély and others.[13–16] In straightforward terms, the model posits a central mechanism providing homeostatic sleep regulation that interacts with the circadian timing mechanism. Anatomic, cellular, and molecular properties of the latter system have been described in great detail, as have the organizing principles of its function.[17] The anatomical structure of the homeostatic process is not yet known, however, nor has the specific nature of the neurochemical or neurocellular basis of this process yet been described, though adenosine regulation,[18] thalamocortical brain oscillations,[19,20] and changes in gene expression[21] have been hypothesized as specific features of the system. Nevertheless, the operational outputs of the homeostatic sleep-wake regulatory system such as quantitative measures of the EEG have been well described (for an overview see Ref. 22), and extensive modeling has successfully predicted outcomes.[23]

In brief, the homeostatic sleep-wake dependent process is modeled as "process S," which accumulates while awake and dissipates during sleep (FIG. 1).[12] Electrophysiological markers of process S include (1) stage 4 NREM sleep also known as slow wave sleep or SWS[24] and (2) EEG power density in the low frequency range (0.75–4.5 Hz) also known as slow wave activity or SWA.[25] The time course of process S delineated from SWA exhibits an exponential decay during sleep and an exponential rise during waking. Sleep occurring after a brief episode of waking (as in a daytime nap) shows relatively little stage 4 and low levels of SWA[26,27] as compared to these features during sleep that follows a normal or extended day length.[25,28] Thus, SWA levels during NREM sleep are determined by the duration of prior sleep and wakefulness. In addition, the speed of falling asleep (sleep latency) has been demonstrated to be a marker for sleep homeostasis.[29] For example, sleep restriction over several nights induces a progressive reduction of sleep latency.[30] Thus, faster sleep onsets can indicate greater accumulation of sleep homeostatic drive, familiar to us all, for example, when witnessing sleep deprived students or colleagues nodding off during the day.

The circadian timing system is essentially independent of prior waking and sleep.[31] It contributes to the timing of sleep by providing signals (the precise neurophysiological nature of which are unknown) interpreted as "sleep gates" occurring at some times and during other phases as "forbidden zones" for sleep.[13,32] Circadian sleep propensity reaches its maximal levels in the early morning and its trough in the

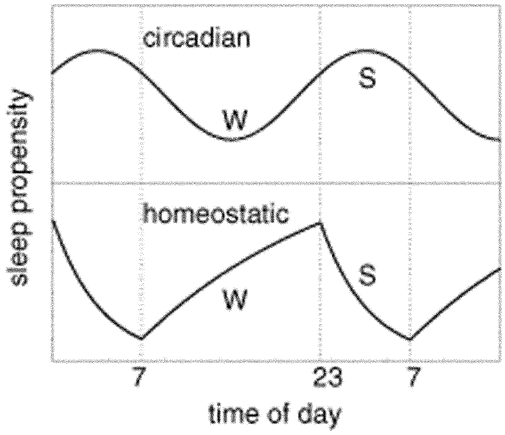

FIGURE 1. Schematic of the circadian and homeostatic process underlying sleep regulation. The rise of the homeostatic process yields a longer time constant then the decay reflecting the unbalanced amount of time spent awake and asleep. W, wakefulness; S, sleep. (Redrawn in part from Achermann & Bobély.[23])

evening (FIG. 1).[31] Current models include a concept in which the homeostatic and circadian systems normally operate as opponent processes that enable the consolidation of sleep and wakefulness.[16,31,33,34] In other words, an increasing circadian drive for arousal during the waking day is proposed to counteract the growing homeostatic sleep pressure in order to maintain the waking state.[14,16,33] Conversely, the declining NREMS sleep intensity or pressure during sleep opposes the increase in circadian sleep tendency across the night thereby maintaining consolidated sleep.[34]

Several additional features of the circadian timing system merit introduction (for an overview see Ref. 17). Although we do not have direct access to the clock mechanism itself in human participants, we are able to measure such parameters of the system as phase, period, amplitude, and phase angle through assessing peripheral signals. The timing of melatonin secretion is one of the most reliable of such measures and is eminently accessible in young humans through radioimmunoassay of melatonin from serial saliva samples. Thus, we can assess the phase of the circadian system as the onset, offset, midpoint, or peak phase of melatonin secretion. Phase preference (when it "feels good" to do various activities) can be assessed using standard self-assessment instruments.[35–37] The intrinsic period of the circadian timing system is more difficult to assess. In rodents, period is inferred from the timing of behaviors (usually wheel-running) over the course of many cycles under conditions of environmental isolation and constant darkness—not a testing environment available for human studies, particularly not for young humans. Instead, a method called forced desynchrony is used, wherein participants stay in the lab for a number of weeks under relatively low light conditions with sleep and waking scheduled at a day length that exceeds the range of entrainment of the circadian timing system, such as 20 or 28 hours.[38,39] Under these circumstances, the circadian timing system runs

free from the sleep–wake process, and the intrinsic period of the rhythm can be assessed through the timing of daily phase markers. Coincidentally, this experimental paradigm is useful for analyses to identify the influences of the homeostatic and circadian processes independent from and interacting with one another.[31]

Our group has begun to apply these principles and methods to examine the development of intrinsic sleep-wake regulatory processes during adolescent development. Our aim is to determine the extent to which these processes undergo predictable changes in association with pubertal development and ultimately to identify how such changes may interact with the behavioral regulation of sleep. Intrinsic changes may either compel or control the adolescent phase delay, or they may be permissive of the phase delay. Thus, for example, a puberty-related delay in circadian phase might prevent older teens from falling asleep early and drive a later time for arousal; or a reduction in the build up rate of process S might permit or ease the way for older teens to stay up late. In addition, an important corollary of these biological systems is that certain aspects of the intrinsic regulatory processes may themselves respond to alterations of sleep and wakefulness associated with behavioral regulation. For example, behaviorally mediated changes in the timing of light–dark exposure directly interact with the phase resetting mechanism of the circadian timing system[40] and can reinforce or strengthen a tendency to phase delay. In this paper, we review findings that address these issues, identify the net effect on sleep patterns, and discuss briefly how the ultimate result of these processes may lay open vulnerable outcomes for adolescents.

THE HOMEOSTATIC PROCESS (PROCESS S) DURING ADOLESCENCE

The developmental alteration in slow wave sleep during adolescence has been known for a number of years. Feinberg[41] showed that SWS declined across the adolescent years using cross-sectional samples, as did the Williams group.[42,43] Karacan and colleagues[44] showed a pubertal decline in SWS in a longitudinal study where sleep was on the participants "usual" schedules, confirmed by Carskadon[45] in a longitudinal study that held sleep time constant. In the Carskadon report,[45] SWS declined by approximately 40% from Tanner stage 1 (ages 10 to 12 years) to Tanner stage 5 (ages 14 to 16 years). The fundamental question arises now whether the decline of SWS is reflected in altered sleep-wake processes as well. Several groups have presented data examining spectral EEG variables including SWA across adolescent development.[46,47] Gaudreau and colleagues,[47] for example, reported a similar nocturnal decline of SWA between children and adolescents.

Our group has begun to examine pubertal changes in the sleep EEG within the context of the homeostatic model. Sleep EEGs in 6 pre- or early pubertal (Tanner 1 or 2, ages 10.3 to 12.8 years, 5 girls) and 6 postpubertal adolescents (Tanner 5, ages 11.8 to 16 years, 3 girls) have been analyzed using spectral analysis.[48] We showed a significant reduction in EEG power density during NREM sleep at frequencies <2 Hz and 4–6 Hz for the mature versus the prepubertal participants. Total power in the low frequency band <2 Hz was reduced by 64% during NREM sleep. Furthermore, we saw an exponential overnight decay of SWA in both groups, with equal time constants of the decaying function. These findings converge to indicate that the homeostatic process involved in the dissipation of process S across sleep under controlled

sleeping conditions does not manifest a maturational change across pubertal development. The substantially lower amount of SWS and low-frequency EEG power across adolescence may rather reflect changes in underlying brain structure (e.g., declining cortical synaptic density) as noted by Feinberg.[49,50]

The accumulation of process S, however, does appear to differ in its expression across adolescent development, based upon preliminary evidence. A test of this process requires assessment of the homeostatic markers under conditions that involve an alteration of the usual daily sleep-wake schedule, such as napping as suggested previously, or sleep deprivation. We have examined the speed of falling asleep (sleep latency) using standard methods in adolescents during 36 hours of sleep deprivation.[51] These data indicate that sleep latencies during initial hours of extended wakefulness were longer in more mature participants than in prepubertal children, indicating that accumulation of process S across the day may occur at a slower rate in more mature adolescents.

Our preliminary analyses of the EEG in the sleep episode following an extended waking interval of 36 hours showed the expected increase in low frequency EEG power during NREMS sleep in both groups.[48] The prepubertal children, however, manifested a less pronounced (30%) average increase of low frequency power comparing recovery to baseline versus the mature adolescents (70%). These data indicate that the younger child's brain quickly reaches the maximal capacity to generate low frequency activity during sleep. We are currently modeling the spectral EEG data from the nights following baseline and extended wakefulness to determine whether parameters that describe the accumulation of process S change as a function of pubertal development. Although the preliminary analysis of the sleep latency data hints at such a developmental change, we do not yet feel confident in drawing this conclusion.

The homeostatic sleep–wake process plays out in another manner when the adolescent delay in the timing of sleep produces chronic insufficient sleep in many youngsters. Chronic sleep restriction becomes manifest when we examine speed of falling asleep.[29] For example, we showed that tenth-grade students with a "first bell" at 7:20 AM were able to fall asleep in fewer than 5 minutes on morning tests of sleep latency, never rising above about 10 minutes; indeed, many showed REM sleep in brief morning naps, coinciding with the time of their second-period class.[11] These data illustrate a powerful effect of homeostatic sleep regulation, as well as the impact of the circadian timing system (vis-à-vis the REM sleep finding). To the extent that the bedtime delay in older adolescents is mediated by intrinsic processes, the requirement for early rising to attend school inevitably results in inadequate sleep.

THE CIRCADIAN TIMING SYSTEM (PROCESS C) DURING ADOLESCENCE

Our interest in the possibility that changes in the intrinsic circadian timing system accompany puberty stemmed from a self-report assessment of pubertal development and circadian phase preference in sixth graders.[37] These data showed that those children (particularly the sixth grade girls) who rated themselves as more physically mature also rated themselves as more "evening" type in their phase preference. We subsequently confirmed this circadian phase delay tendency in a laboratory study in

which Tanner stage was assessed by physician evaluations and circadian phase was measured by salivary melatonin[a] levels. Again, pubertal stage correlated with the circadian phase marker, such that more mature children showed a later phase of melatonin secretion offset.[52] We here also report that melatonin onset phase measured in 27 adolescents after controlled sleep-wake schedules was positively correlated with Tanner stage ($r = .54$; $P = .003$). These findings provide convergent evidence that circadian phase undergoes a delay in association with puberty, even under conditions controlling for psychosocial influences on sleep-wake patterns.

We should note that an alteration of the amplitude of the daily melatonin secretory patterns across pubertal development has been known for many years. A decline in nocturnal plasma melatonin levels across puberty was shown in cross sectional samples.[53,54] This decline was initially thought to be part of the hormonal cascade initiating pubertal development. In fact, the earliest reports of the reduction of melatonin secretion in pubertal children led to a speculation that melatonin was a "trigger" for puberty,[55] which was disputed strongly by others (cf. Ref. 56). Other reports, however, indicated that no change occurred in total excretion of the melatonin urinary metabolite, 6-hydroxymelatonin sulfate (6-OHMS), across puberty. The pubertal change in plasma melatonin levels was attributed to a change in the distribution of secreted melatonin in the larger body mass of the more mature adolescents with no change in the production of melatonin per se.[57] Recently, Griefahn and colleagues[58] examined urinary 6-OHMS excretion in a longitudinal sample. Their data lead to the interpretation that body size is the mediating factor for the pubertal decline in plasma melatonin levels, not falling melatonin secretion. No studies are available that have assessed plasma and urinary concentrations of melatonin simultaneously.

We recently analyzed data from a cross-sectional sample of adolescents in whom salivary melatonin was collected at 30-minute intervals across 18 hours during a "constant routine" protocol.[59] The salivary melatonin profiles of 14 participants (ages 9.6 to 12.9 years, 7 girls) at Tanner stage 1 and 12 participants (ages 11.8 to 14.4 years, 6 girls) at Tanner stage 5 were collected. Linear regression analysis of melatonin levels (area under the curve) and amplitude (maximum) including age, body mass index, phase preference, and Tanner stage, showed a significant contribution only for Tanner stage. Furthermore, we found (as have others[60–62]) large individual differences in melatonin levels. Our analyses, based on data collected under very controlled conditions of sleep timing, again raise the possibility that pineal secretion of melatonin declines during pubertal development. We can only speculate that this developmental change—whether mediated centrally or by secondary developmental characteristics such as body size—may signal a pubertal reduction in feedback of melatonin to the circadian timing system, which could alter the circadian signal to the sleep-wake system.[63] Shanahan[64] hypothesized, for example, that low melatonin

[a]Pineal melatonin secretion is controlled by the circadian timing mechanism (and feeds back on this system) to rise during the brain's nighttime and nearly cease during the daytime of the brain. Hence, melatonin has been dubbed the "hormone of darkness." Melatonin secretion can be suppressed by light, and such suppression is thought to be one indicator of the extent to which light affects the timing system. We use melatonin levels to mark internal time as the "hands" of the intrinsic circadian clock.

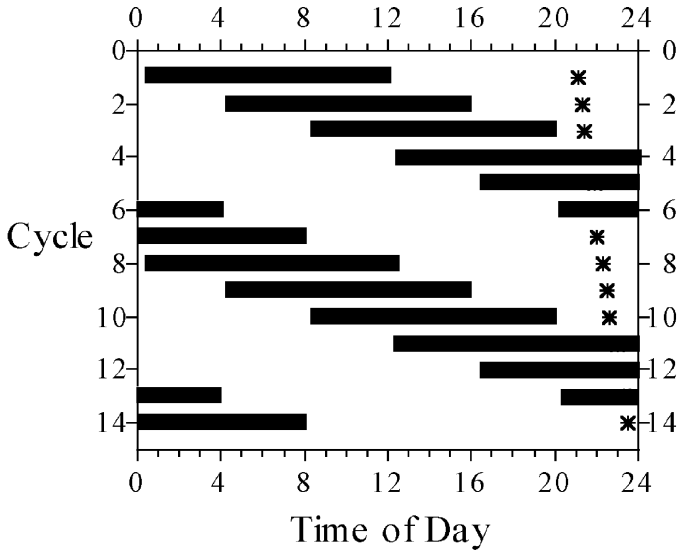

FIGURE 2. Schematic of the forced desynchrony protocol. Scheduled sleep episodes (*black bars*) are shown for a 28-hour day length for 14 consecutive cycles. Participants live in the laboratory under dim light conditions (~15 lux) so that dim-light melatonin onset (DLMO) can be determined from serial saliva samples. A hypothetical pattern of DLMO is shown by the *star symbols*, indicating that the circadian timing system is running free of the 28-hour day length at a period of about 24.2 hours.

amplitude reflects a diminished amplitude of the light-sensitive endogenous circadian pacemaker. Perhaps decreased melatonin amplitude in older adolescents plays a role in their tendency to manifest a delayed sleep phase.

Another mechanism predicted by circadian rhythms models is that a delay of circadian phase may be related to a lengthening of the period of the circadian clock, that is, a longer internal day length.[65] Under normal day-to-day circumstances, features of the environment that have a 24-hour period, particularly the light-dark cycle, entrain the internal clock to 24 hours. The phase angle with which the internal clock time aligns with the external day, however, is determined in part by the intrinsic circadian period: the phase angle of entrainment is delayed in parallel with the extent to which the internal day length exceeds 24 hours. Thus, we predicted that period of the circadian timing system may lengthen during puberty.

As mentioned previously, the method for measuring period is a bit arduous, involving prolonged laboratory stays under carefully controlled conditions. FIGURE 2 illustrates an experimental protocol we have used to assess period in adolescents by collecting serial measures of salivary melatonin onset and offset across 12 cycles on a 28-hour day(i.e., forced desynchrony). Our initial analysis of intrinsic period in adolescents showed that period appeared longer than reported by others in young adults, but we did not have adequate numbers of subjects to test the pubertal hypothesis.[66] We present here data from 27 participants who have completed the forced de-

synchrony protocol. We found no evidence of a pubertal change in period in this still rather small cross-sectional sample, but hope to acquire longitudinal data in order to re-examine this hypothesis. One of the major limitations of studying this phenomenon is the difficulty in making the measure in truly prepubertal participants because of the lengthy commitment to the laboratory stay. We compared the distribution of intrinsic period in our sample with samples of adults in whom period was also derived from melatonin phase markers in a 28-hour forced desynchrony paradigm.[67,68] The mean period of the circadian clock in adolescent participants (24.27 h) is significantly longer than in the adult samples (24.12 h). These comparisons are not conclusive, rather they are suggestive that longer internal day lengths may emerge in certain adolescents.

Another important feature of the circadian timing system is the phase-dependent sensitivity to light intrinsic to the clock resetting process.[69] Light occurring in the early part of the circadian night (evening and early nighttime) produces a delay resetting response in the clock, whereas light signals in the late night/early morning result in an advance resetting response (cf. Ref. 70). One marker of the effects of light on the circadian timing system is the suppression of melatonin levels by light.[40] We have hypothesized that the sensitivity of the circadian system to light may change during pubertal development in a manner that accentuates the tendency for a phase delay and have tested the hypothesis using melatonin suppression.[71] In brief, we suggest that a heightened sensitivity to evening light or a decreased sensitivity to morning light across pubertal development could result in the pubertal delay of sleep timing. An assessment of this hypothesis in 66 participants who received 4 levels of light on consecutive nights either in the late evening or early morning showed greater suppression to a low level of light administered in the morning for pre- and early pubertal participants than for late or postpubertal participants, and no differences in response to late night light.[72] These findings provide suggestive support for the hypothesis.

On the other hand, the most relevant assessment of the circadian response to light is actual phase realignment response to light signals. Thus, to what extent does the circadian timing mechanism actually reset its phase when an adequate light signal is given? We are currently evaluating this process by exposing adolescents who are Tanner stage 1 or Tanner stage 5 to a 2-hour light signal of 3,000 lux on two consecutive days. We administer light at times where the phase response curve predicts either a phase resetting delay or a phase resetting advance. Ultimately, we propose to acquire data across the entire phase response curve (PRC) for pre- and postpubertal adolescents, hypothesizing that the amplitude of the phase-resetting responses will be greater in the delaying direction or smaller in the advancing direction for the more mature group. If such developmental changes in PRC are operational, the permissive/responsive interaction of the behavioral and biological processes could set up a synergistic increase in pressure for adolescents to phase delay.

INTERACTION OF THE HOMEOSTATIC AND CIRCADIAN PROCESSES DURING ADOLESCENT DEVELOPMENT

A number of findings predict that a critical developmental outcome during adolescence may be a change in the phase angle of the homeostatic to the circadian tim-

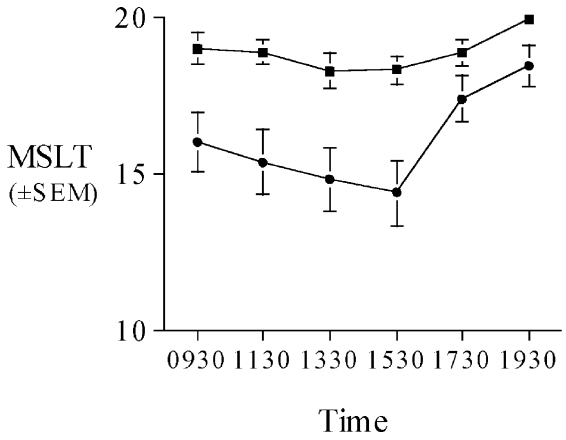

FIGURE 3. Sleep latency from Multiple Sleep Latency Tests (MSLT) in 25 pre-/early pubertal (Tanner stages 1 or 2; *squares*) and 27 mid-/late pubertal (Tanner stages 3, 4, or 5; *circles*) participants in a longitudinal sleep study.[29] Mean (± standard error) of sleep onset latencies indicate speed of falling asleep on tests scheduled at 2-hour intervals after 10-h nocturnal sleep episodes. More-mature participants fell asleep faster on the tests at 1530 and 1730, indicating augmented midday sleep tendency in spite of sleeping the same amount at night.[30]

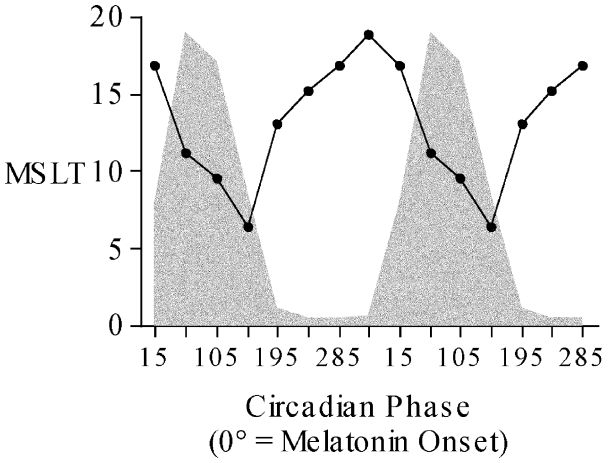

FIGURE 4. Circadian rhythm of sleep tendency as measured by MSLT on the background of averaged melatonin secretion (*gray shading*) from 10 adolescents studied in a 28-hour FD. The pattern displayed here is derived by averaging data from particular circadian phases (determined by the melatonin phase marker) irrespective of time awake.[74] As indicated in the text, the pattern appears paradoxical, since shortest sleep latency occurs at the end of the circadian night and long sleep latencies at the beginning of the circadian night. The rising latencies in the circadian day are conceptualized as indicating a clock-dependent alerting signal.

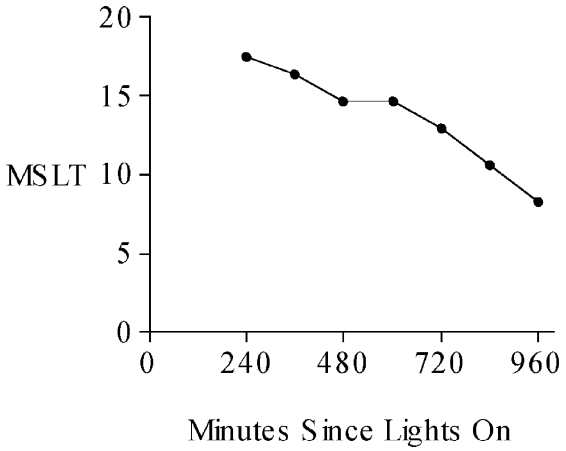

FIGURE 5. The MSLT sleep tendency pattern from the study described in the legend for FIG. 4 was derived by the average of sleep latencies in reference to the length of time a participant was awake regardless of circadian phase.[74] This curve is conceptualized to indicate the homeostatic process accumulating as a growing sleep propensity across the waking day. As described in the text, the pattern of sleep propensity across an individual's waking day will depend upon the phase alignment of sleep/wake to the circadian timing system. Alterations of this phase alignment can facilitate late bedtimes when clock-dependent alerting rises late in the day. On the flip side, the phase angle of entrainment favoring late bedtime also is associated with difficulty waking in the morning.[74]

ing system. One of our earliest findings regarding sleep tendency during puberty[73] demonstrated a paradoxical increase in sleep tendency in adolescence at mid- to late puberty compared to pre- or early puberty. FIGURE 3 illustrates this finding, which was initially interpreted as an increase in sleep pressure, even though total sleep time had not changed. We also speculated that the changed pattern of diurnal sleep tendency might indicate a reorganization of central behavioral organization, for example, to favor a "siesta" in more mature humans.[73]

Recent conceptual advances in combination with data acquired in the context of forced desynchrony allow us to reinterpret this finding as a pubertal change in the phase angle of entrainment of sleep and waking to the circadian timing system.[74] We have shown, for example, that each of the two systems—when examined in isolation—provides counterintuitive findings with regard to circadian timing. As FIGURE 4 illustrates, the circadian signal demonstrates fastest sleep onsets (greatest sleep tendency) at the end of the circadian night (inferred from the melatonin secretory pattern) and slowest at the start of the circadian night. Taken at face value, however, these data are paradoxical, since most would assume that humans should fall asleep fastest at the beginning of the night rather than at night's end. The homeostatic process when examined separately from the circadian rhythm, builds to greater sleep tendency across time, thus faster sleep onsets occur the longer one is awake (FIGURE 5). Alignment of these two processes, however, as occurs during normally entrained

conditions, solves the paradox: the circadian system, through "clock-dependent alerting," offsets the growing homeostatic pressure across the waking day. This association describes graphically the competing nature of these processes as described earlier.[74]

What is also apparent is that the alignment of these two processes will affect the balance of the two processes across the day. Thus, we now interpret our earlier findings of augmented midday sleep tendency in pubertal adolescents[73] to indicate a reorganization of the phase relationship of these processes. The mechanism underlying this realignment is not known, but it may be determined by the factors outlined above, such as alterations of intrinsic period or phase resetting properties of the clock mechanism. If the phase angle becomes realigned during late puberty, then the clock-dependent alerting later in the day can facilitate late sleep onset. Similarly, this phase realignment may manifest as a significant increase in the difficulty of waking in the morning. As more is learned about these underlying mechanisms and their association to the multiple behavioral influences on adolescent sleep timing, we may gain insights into opportunities for intervention.

CONSEQUENCES OF THE SLEEP DELAY FOR ADOLESCENT BEHAVIOR

In the United States in particular, as well as in a few other industrialized societies, the changing adolescent sleep–wake system exists in the context of a relatively unforgiving educational structure demanding earlier school attendance in older than younger children. Whether the delay of the timing of sleep in adolescents is exclusively attributable to the psychosocial milieu or receives contributions from changes in the intrinsic regulatory processes, we observe inadequate and ill-timed sleep in a large number, if not a majority of young people. Our group has found, for example, that the estimated amount of sleep accumulated during the school week in youngsters in grade 6 averages 500 minutes, in grade 8 is 473,[75] and in grade 10, the average is 452 and grade 12, 420 minutes based upon objective monitoring in the field. Laboratory data indicates that the sleep need in these youngsters is closer to 555 minutes per night.[45,76]

As we learn more about the effects of chronic insufficient sleep, concerns grow about the potential for negative impacts on adolescents. For example, rates of automobile crashes attributed to falling asleep while driving are markedly higher for the youngest drivers. Indeed, a retrospective analysis of over 4000 such occurrences showed that the drivers' ages in just over 50% of crashes were 16 to 25 years.[77] Growing evidence also indicates that adequate sleep plays an important role in memory consolidation and learning processes,[78–80] though research specific to adolescents is scarce. The preponderance of evidence from a variety of studies examining the association of sleep patterns with academic performance indicates that too little and poorly timed sleep has a negative impact in children, adolescents, and young adults.[81] Furthermore, tardiness, absenteeism, and high school graduation rates in adolescent students have been linked to sleep schedules and early school starting times.[82]

Mood regulation also suffers with inadequate sleep. Time and again, our studies—whether observational or experimental—have found depressed mood at greater

rates in young people whose sleep is compromised (see Ref. 2, for example). Behavior disruption has also been noted as a concomitant of disturbed sleep in children with sleep disorders [83–86]; less is known about this association in adolescents.

Substance use, including caffeine, alcohol, and tobacco, is also greater in teens who sleep less.[87,88] Recent data in adults show that sleep is not simply for the mind, but affects metabolic processes as well.[89] Indeed, one epidemiologic study linked adolescent obesity with poor sleep patterns.[90] As sleep patterns are examined along with other lifestyle or medical outcomes, we can anticipate more negative associations of poor sleep to become apparent.

CONCLUSION

The robust tendency for the timing of sleep to delay during adolescent development is undeniably associated with the changed psychosocial environment of the developing teen and may also rely on developmental changes in fundamental regulatory processes. For many teens, this sleep delaying pattern cascades into a chronic pattern of insufficient school-day sleep, forced arousals at a biologically inappropriate time, and resulting negative impacts on adolescent performance, behavior, mood, and other processes. Countermeasures that are implemented on a personal, family, community, or societal level need to acknowledge all the factors contributing to the issue. We feel that primary among the countermeasures is an acknowledgement of a positive priority for sleep and a need for a better understanding of the sleep-wake regulatory process through education and research.

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Patterns of Sleep and Sleepiness in Adolescents

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Abstract. Most studies of adolescent sleep habits show a pattern of decreasing total sleep time, a tendency to delay the timing of sleep, and an increased level of daytime sleepiness. Laboratory tests have shown that adolescents do not have a decreased need for sleep but probably need *more* sleep than prepubertally. A number of factors affect the development of adolescent sleep patterns. Puberty itself imposes a burden of increased daytime sleepiness with no change in nocturnal sleep. Parental involvement in setting bedtimes wanes, though they become increasingly involved in waking teenagers in the mornings. Curfews and school schedules also affect adolescent sleep patterns, seen most commonly as imposing earlier rise times as the school day begins earlier during the adolescent years. Part-time employment has a significant impact on the sleep patterns of teenagers: those who work more than 20 h each week sleep less, go to bed later, are more sleepy, and drink more caffeine and alcohol. Development of circadian rhythms may also play a role in the phase delay teenagers commonly experience. The primary conclusion is that many adolescents do not get enough sleep. The consequences of the chronic pattern of insufficient sleep are daytime sleepiness, vulnerability to catastrophic accidents, mood and behavior problems, increased vulnerability to drugs and alcohol, and development of major disorders of the sleep/wake cycle. Educational programs hold the promise of improving teenagers' sleep patterns through informing youngsters, parents, and pediatricians about proper sleep hygiene and the risks of poor sleep habits.

Introduction

Among the multiplicity of changes that accompany adolescence are alterations in sleeping and waking patterns [1]. These changes arise from a number of sources: changing academic demands, expanding social opportunities, altered parent-child relationships, involvement in part-time jobs, increased access to drugs and alcohol, etc. Also important among factors resulting in changing adolescent sleep patterns are physiological processes [2]. Very few studies have directly examined specific factors that might influence the development of adolescent sleep patterns. As will be shown below, empirical studies may call into question the conventional wisdom. For example, it is a common perception and also a societal expectation that adolescents do not really *need* as much sleep as preadolescents. Our sleep laboratory data, however, suggest that older adolescents may actually have a physiological need for *more* sleep than preadolescents, not *less*. The cultural patterns in North America that promote shortened nocturnal sleep in teenagers conflict with the physiological imperatives requiring increased nocturnal sleep. Thus, adolescents may become increasingly at risk for excessive sleepiness, dysphoric mood, or even catastrophic accidents as a result of excessive daytime sleepiness [3].

Sleep/Wake Patterns in Adolescents

Let us begin by inspecting what adolescents say about their sleep. Self-reported sleep/wake patterns of adolescents have been investigated by a number of groups, primarily using cross-sectional sleep habits surveys [4–15].

Table 1. Self-reported sleep patterns in adolescents

	Age	Girls			Boys		
		bedtime	risetime	sleep time	bedtime	risetime	sleep time
School nights	10[1]	9:30	7:15	9h 45m	9:09	7:00	9h 51m
	11[1]	9:30	7:05	9h 35m	9:40	7:00	9h 20m
	12[1]	9:45	6:55	9h 10m	9:50	7:05	9h 15m
	13[1]	10:06	6:50	8h 44m	10:28	7:00	8h 32m
	14[2]	10:10	5:56	7h 46m	10:16	6:15	7h 59m
	15[2]	10:24	6:05	7h 41m	10:43	6:27	7h 44m
	16[2]	10:52	6:13	7h 21m	11:08	6:38	7h 30m
	17[2]	10:58	6:26	7h 28m	11:14	6:45	7h 31m
	18[3]	1:15 a.m.	8:18	7h 3m	1:30 a.m.	8:36	7h 6m
Weekend nights	10[1]	10:25	8:10	9h 45m	10:22	7:45	9h 23m
	11[1]	10:22	8:25	9h 3m	10:50	7:45	8h 55m
	12[1]	10:55	8:35	9h 40m	11:05	8:35	9h 40m
	13[1]	11:20	8:45	9h 25m	11:42	8:45	9h 3m
	14[2]	11:57	9:14	9h 17m	12:06 a.m.	9:12	9h 6m
	15[2]	12:11 a.m.	9:24	9h 13m	12:27 a.m.	9:25	8h 58m
	16[2]	12:28 a.m.	9:21	8h 53m	12:44 a.m.	9:37	8h 52m
	17[2]	12:39 a.m.	9:21	8h 42m	12:51 a.m.	9:29	8h 38m
	18[3]	2:48 a.m.	10:39	7h 51m	2:43 a.m.	10:40	7h 57m

[1,2] From previous surveys [8, 12].
[3] From college freshmen [18].

Two longitudinal survey studies [16, 17] have also been reported. The study of Strauch and Meier [17] is the most comprehensive longitudinal survey, covering a 10-year period (1975–1985) with surveys at 2-year intervals in a pool of 100–190 German (FRG) adolescents who were aged 10–14 years at the study inception. The cross-sectional surveys have focused primarily on somewhat narrow age ranges. Table 1 presents a representative sample of data about adolescent sleep by combining data from several of our surveys of youngsters attending public school [8, 12, 18]. As will become clear in subsequent sections, a number of factors influence such 'norms'.

Several major trends emerge from the various survey studies. First, self-reported nocturnal sleep time declines across the adolescent span. Second, bedtimes during high school grow later and rising times earlier. Furthermore, teenagers show increasingly large variations between weeknight and weekend sleep schedules. The Strauch and Meier [17] data, for example, showed that weekend sleep times averaged about 30 min less than weeknight sleep time in the 10- to 14-year-olds, and the difference increased to over 2 h by age 18 years. The timing of sleep on weekdays versus weekends also shows progressively greater variability across the second decade. For example, our survey of young adolescents [8] showed about an hour's weekend-weeknight difference in 10-year-olds, increasing to about 90 min at age 13. More recently, we have found rise time reports in high school students to average approximately 3 h later on weekends than on weekdays. In college freshmen, bedtimes and rise times both slide to later times on weekdays as well as weekends [18]. Given this background, let us now examine what is known about a number of the factors that affect adolescent sleep/wake patterns.

Factors Affecting Adolescent Sleep/Wake Pattern Development

Puberty

The effects of pubertal maturation were examined in a longitudinal study that looked at sleeping patterns and daytime alertness using sleep laboratory measures [1, 2, 19]. For this study, 27 normal control children (12 girls and 15 boys) were studied on a total of 109 sessions over the course of 7 days. (Only a few returned for all 7 years; 21 were studied on at least three occasions.) During each session, the adolescent received a 72-hour (3 nights and 3

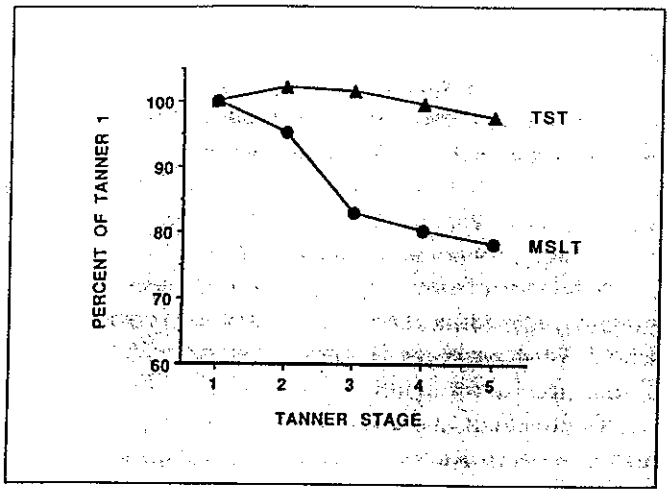


Fig. 1. This figure summarizes data from a 7-year longitudinal study of adolescent sleep and sleepiness, as described in the text. Data are grouped by Tanner stages and presented as a percentage of the Tanner stage 1 (prepubertal) average. Triangular symbols show the values for TST and round symbols show daily mean MSLT scores. TST showed no significant change from the Tanner 1 mean (about 9h 10m) across the Tanner stages, whereas MSLT declined significantly at Tanner stage 3 and remained low in Tanner stages 4 and 5. This finding suggests that older teens may have a physiological need for more sleep than younger adolescents.

days) evaluation at 'Sleep Camp'. The evaluation included overnight sleep recordings and daily measurements of daytime sleepiness using the Multiple Sleep Latency Test (MSLT) [20]. Maturational status was assessed using Tanner staging [21]. Overnight sleep recordings (with electroencephalogram, electro-oculogram, and electromyogram for analyzing sleep stages) were made on a constant schedule – 10:00 p.m. until 8:00 a.m. – across all years of the study. The MSLT measures daytime sleepiness as the speed of falling asleep based on physiological activity. Measures are taken at 2-hour intervals in a rigorous, standardized manner [20]. This test is now the most common measure for evaluating daytime sleepiness in experimental or clinical settings [22]. Tanner stages of maturation range from Tanner 1 – which reflects a prepubertal child – through intermediate pubertal development (Tanner stages 2, 3, and 4) to Tanner 5, the fully mature adolescent.

Figure 1 summarizes the relationships of nocturnal sleep patterns and daytime sleepiness to maturational level found in this longitudinal study. Two important findings stand out. First, the total amount of sleep (TST) at night remained constant across the developmental stages. Second, the MSLT showed a clear relationship to maturational stage, with a significant increase in sleep tendency during the daytime (greater sleepiness) at Tanner stages 3, 4, and 5. The children at Tanner stages 1 and 2 rarely fell asleep on this test. These findings were consistent across gender. It is important to keep in mind that the average TST at night was virtually identical for subjects at each Tanner stage, as figure 1 shows. Thus, the change in daytime sleep tendency across maturational stage was *not* related to a change in the amount of sleep at night. The implication of this study is that older adolescents become sleepy in the daytime, *even* when sleeping as much as younger adolescents. Therefore, if anything, older teens may *require more* sleep to maintain alertness than do younger teens.

Parental Influence

Among environmental factors that appear to influence the development of sleep/wake patterns early during adolescence is a change in the way parents regulate a child's sleep. Figure 2 illustrates the trends obtained in our survey of a younger adolescent group [10]. First, over half of the 10-year-old children reported that their parents set their bedtimes on school nights; by age 13, only 19% of parents set school-night bedtimes. Second, 19% of parents of 10-year-olds set bedtimes weekend nights, declining to 4% of the parents of 13-year-olds. Finally, rising times on school mornings were initiated by a parent or alarm in fewer than half the 10-year-olds versus 70% of 13-year-olds. These data suggested to us that one major early change in the organization of sleep/wake behavior in adolescents is an alteration in the nature of parental influences: parents of children and younger adolescents direct their attention to bedtime; in older adolescents, parental influence diminishes at bedtime and becomes more important to waking up.

Curfews

A related issue was examined by evaluating sleep/wake patterns in 9th and 10th grade students attending boarding schools with and without set curfews [23]. An interesting pattern of findings arose from this evaluation. First, as one would expect, the students given a curfew reported going to bed about an hour earlier on average than those with no curfew. Second, regardless of whether or not a curfew was imposed, all students in this study slept about the same amount on school nights (average = 7 h 15 min). Thus, even though the regulatory influence was present only at bedtime, the students who had a curfew also tended to get up about an hour earlier

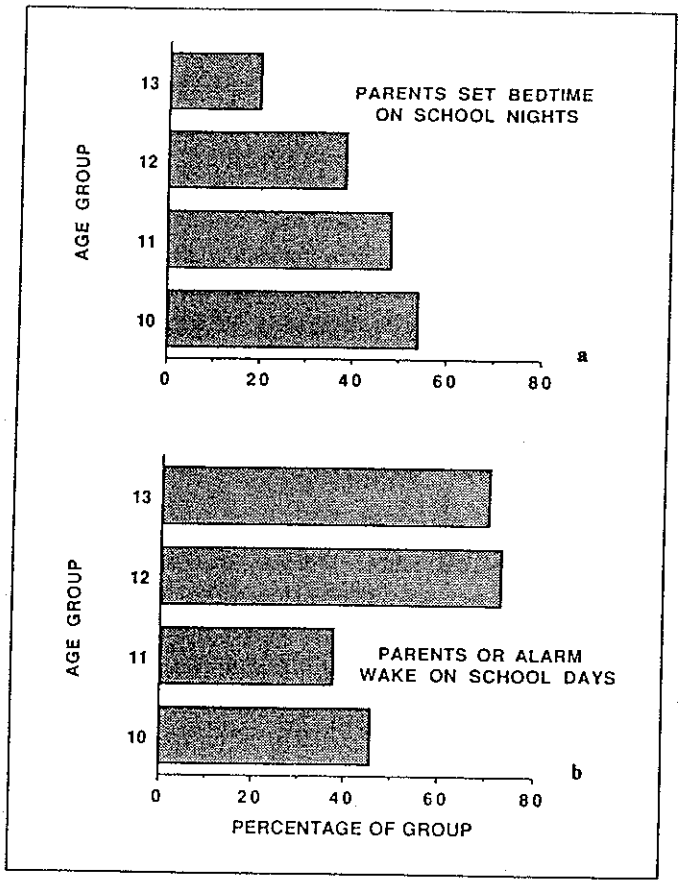


Fig. 2. This figure summarizes questionnaire response data from youngsters aged 10–13 years to questions asking what factor determines why they go to bed (a) and get up (b) on school mornings [10]. By age 13, less than 20% of the group reported that parents set their bedtimes. By age 12, over 70% of the group reported that they no longer wake spontaneously but required an alarm or parental awakening.

in the morning. Finally, the students with a curfew – those going to bed and getting up earlier – reported fewer symptoms of excessive sleepiness. Here again, it is clear that external agencies (or their absence) have a significant influence on adolescent sleep pattern.

School Schedules

The time that school begins in the morning has an obvious impact on setting sleep/wake schedules in adolescents, presumably strongest in its effect on the time youngsters arise in the morning. For example, the usual pattern in most public school districts call for earlier morning school sessions and consequently earlier rising times in older adolescents. Our data suggest that adolescents tend gradually to adjust to shifts in school start time over a series of years by narrowing the interval between getting up and going to school (table 1). The pattern of later rising times on weekend mornings also suggests that the school schedule impinges on the regulation of sleep/wake patterns on school mornings. Of course, as noted below, the weekday/weekend patterns may also be a response to insufficient sleep.

Another indication of the importance of the school schedule arises from our comparison of sleep habits in students attending private residential versus public school. We have recently surveyed about 1,500 students at four private residential high schools in Massachusetts and Connecticut and about 3,100 students in six public high schools in Rhode Island. One quite notable difference between the sleep patterns of public and private school (noncurfew) students was that public school students consistently reported going to bed and rising earlier (approx. 1 h) than private school students. This difference appears to relate to the differential commute distances; the private school students could all walk to their first morning class, whereas many of the public school students commuted by car or bus.

Jobs

Within the public high school survey population, part-time jobs appear to have a very strong influence on the sleep/wake patterns of adolescents. The sleep patterns of students who report working 20 or more hours per week (high-work) differ greatly from those who report working fewer than 20 h or not at all (low-work) [3, 24]. Table 2 presents several of the variables on which these groups differed. To summarize, the high-work students stayed up later and slept less than the low-work group on school nights and weekend nights. The high-work group also reported more symptoms of daytime sleepiness, including a greater tendency to get to school late because of oversleeping and greater difficulty staying awake in school. The high-work group also reported greater use of caffeine, alcohol, and tobacco. The high-work group comprised over one-quarter of the public high school sample. Thus, a pattern of low sleeping times, excessive sleepiness, and increased substance use may affect large numbers of students. There is a smaller number (4%) in whom the pattern is even more extreme: this is the group of students who work 20 h or more every week and who also take part in extracurricular activities 20+ h each week [3]. These teenagers report a chronic pattern of extremely short sleep along with symptoms of daytime sleepiness and increased use of stimulants and alcohol.

Table 2. Percentage of 11th and 12th graders reporting responses as a function of time spent on jobs

Response	Girls		Boys	
	low-work	high-work	low-work	high-work
School-night bedtime after 11:00 p.m.	18.0	27.9	24.5	40.9
Weekend bedtime after 1:00 a.m.	27.6	37.6	32.9	50.0
School-day rising time after 6:00 a.m.	44.8	45.7	73.3	72.1
Weekend rising time after 10:00 a.m.	30.1	29.0	32.4	30.1
Stay up past 3:00 a.m. at least once a week	18.1	24.0	22.9	34.6
Oversleep and arrive late for school at least once a week	12.9	13.4	11.7	20.4
Fall asleep in the morning at school at least once a week	15.6	18.8	19.5	28.0
Fall asleep in the afternoon at school at least once a week	18.2	23.2	20.1	24.1
Struggle to stay awake or fall asleep doing homework	21.9	27.9	15.3	23.1
Drink coffee or tea every day	18.8	28.1	12.6	22.8
Drink caffeinated soda pop every day	55.8	55.7	52.8	60.4
Drink alcohol every week	15.5	18.4	16.7	25.5
Smoke cigarettes every day	24.4	33.9	14.0	26.4

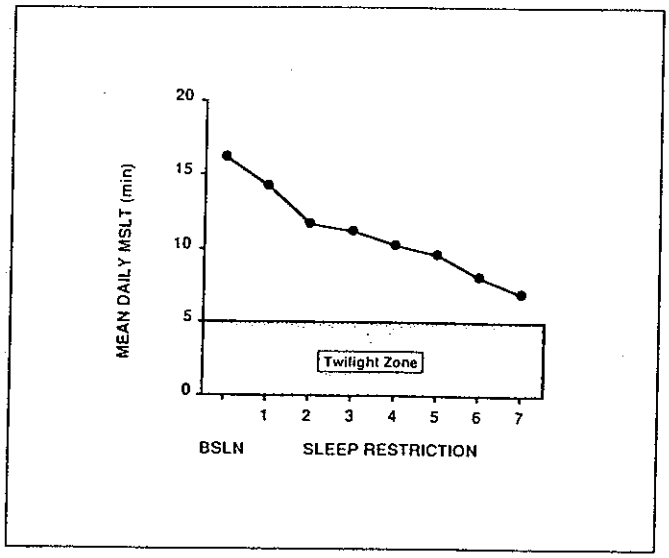
Circadian Rhythms

Another factor that emerges from currently available data – and may be related to a number of the factors above as well as to physiological processes involved in regulating and organizing circadian rhythms – is a tendency for older teens to delay sleep onset. In the first place, there seems to be a simple desire on the part of teenagers to stay up late. For example, Price et al. [9] noted that nearly two-thirds of 11th and 12th graders report that they 'enjoy staying up at night'. This is supported by data from across our various surveys [8, 12, 18] in which we have found a migration of bedtime on school nights from an average of about 9:00–9:30 p.m. in 10-year-olds, to 10:00–10:30 p.m. in 13-year-olds, to 11:00 p.m.–midnight in 17-year-old high school seniors, to 1:00–2:00 a.m. in 18-year-old college freshmen. In the younger groups, the reduction of bedtime setting by parents probably influences the bedtime shift. Other data suggest that the delay may reflect additional environmental circumstance, as well as the adolescent's freedom to self-select bedtime. Thus, as noted previously, when bedtime reports are compared between students who live at home or board at school [25], or between boarding students with and without a curfew [23], or in the high school-to-college transition [18], we find trends for bedtimes to be later in the 'freer' environment. Peer influences and socialization are also likely to be significant factors in this process.

Cross-sectional data from our high school survey, as well as longitudinal data from our high school-to-college transition study [18], also show a progressive change in morningness/eveningness [26] scores, favoring greater numbers of 'evening' types in the older students. The morningness/eveningness or 'lark/owl' score is a measure of 'circadian type' that reflects the time of day at which an individual reports peak functioning. Such scores are related to sleep/wake patterns, as well as other daily rhythms, such as body temperature and food intake [27]. It is not clear, however, whether they measure a *response* to changing sleep/wake habits initiated by other factors or an alteration in the circadian rhythms driving the trend for delayed sleep/wake schedules in adolescence.

Insufficient Sleep and Daytime Sleepiness

By far the most striking conclusion from the available information about adolescent sleep is that many adolescents do not get enough sleep. School schedules require waking up earlier and earlier, while academic work loads, social obligations, and work patterns obligate staying up later and later. Compressed between these daily bookends is an increasingly narrow window for sleep. What happens when sleep is chronically below an optimal level? In one experiment, we looked at this issue in a group of 10 college students [28]. To study their response, we brought them into the sleep laboratory for 10 nights. On the first 3 nights, we allowed them to sleep 10 h; then we reduced their sleep window to 5 h a night for the next 7 nights. Figure 3 illustrates the impact of this sleep restriction pattern on sleepiness as measured using the MSLT. The effect across the 7 days following



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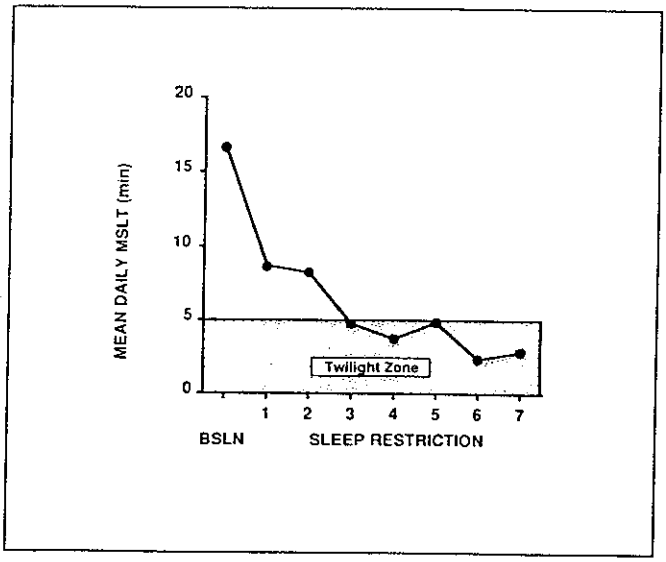

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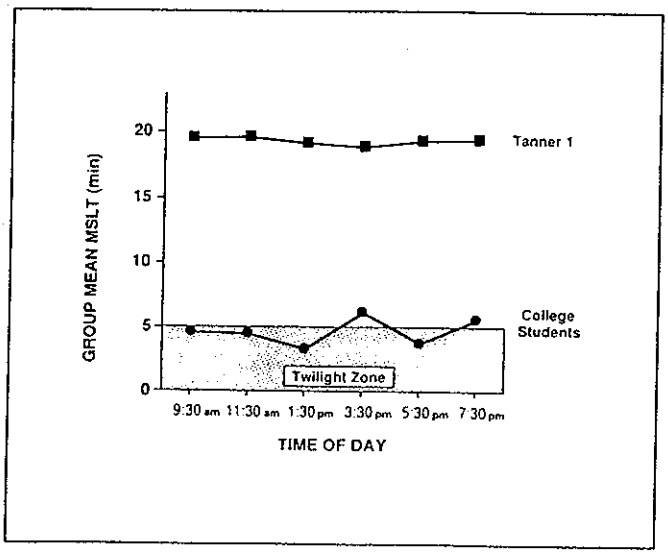

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short sleep was additive; that is, the students got progressively more sleepy every day. Figure 4 shows the example of 1 student who actually became very sleepy on the day after the first short night and was extremely sleepy for the final 5 days. The 'twilight zone' shown in this figure corresponds to a score of 5 min or less on the MSLT, which has been shown to be associated with impaired performance in a number of studies [28–32]. All but 1 of the subjects in this sleep restriction study [28] were in the 'twilight zone' at some point, most for significant portions of every day.

The pattern that we see emerging from all this information is a twofold process that results in a significant level of daytime sleepiness in adolescents. First – whatever combinations of factors may be involved – there is trend for shorter and shorter sleep times across the adolescent span. In addition, puberty produces daytime sleepiness, even when sleep time does not change. Insufficient sleep, therefore, exacts an extra penalty during adolescence. Figure 5 compares sleepiness levels of a group of prepubertal (Tanner stage 1) youngsters sleeping their usual schedule (about 9.5 h a night) and a group of typical college students sleeping their usual 7 h a night. The contrast is striking: the children are maximally alert throughout the day, whereas the combination of factors – pubertal changes plus chronic insufficient sleep – puts the college students in the 'twilight zone' nearly all day long.

Fig. 3. MSLT data from a week-long sleep restriction protocol are summarized in this figure, taken from a study of 10 young adult college students asked to sleep 10 h a night for 3 nights followed by 5 h a night for 7 nights [28]. Baseline results are collapsed into the first data point (BSLN), which shows a high level of alertness before the sleep restriction. As measured by MSLT, sleepiness increased linearly with successive days of sleep restriction. These data highlight the additive impact of chronic sleep restriction.

Fig. 4. MSLT data from an 18-year-old male subject from the study presented in figure 3 are shown in this figure. This young man was very alert during baseline but became very sleepy after 1 night of sleep restriction. After 3 nights, he was extremely sleepy throughout the day and susceptible to lapses and performance decrements, as indicated by the 'twilight zone'. As shown in the summary figure, the decline in alertness was progressive across the sleep restriction days. In this subject, chronic sleep restriction might result in severe impairment.

Fig. 5. This figure summarizes the dual impact of pubertal changes and chronic sleep restriction by juxtaposing average MSLT profiles of children (ages 10–14 years, mean = 11.6) versus college students (ages 18–21, mean = 19.2). The children slept a little more than 9 h a night, whereas the college students slept about 7 h.

Adolescents are clearly variously affected by these factors, but it is important to realize that excessive sleepiness is a potentially serious problem. The scope of the problem has been paradoxically unrecognized in part because adolescent sleepiness is so widespread and obvious (observe any high school or college classroom) that it almost seems to be normal. Yet its consequences, if often subtle, are very real. To the extent that a teenager is excessively sleepy, he or she has an increased vulnerability to a number of poor outcomes. Excessive sleepiness, as mentioned above, is associated with performance failures and lapses. Such lapses impact unfavorably on learning and potentially catastrophically on such activities as automobile driving. The sleepy teenager is also at potentially greater risk to abuse drugs in an attempt to increase alertness by self-medication with caffeine and more potent stimulants. We have also noted evidence that increased alcohol use is related to insufficient sleep in teens, at least in the context of our high-work group. An additional risk arises because of the recently described synergistic interaction of hypersomnolence and alcohol, potentiating the sedative effects of alcohol [33–35]. The relationship of alcohol and insufficient sleep may be particularly hazardous for teenagers, due to the well-known tendency for adolescents to engage in experimentation with alcohol and other risk-taking behaviors. In this context, sleepiness may reduce an adolescent's safety margin for such experimentation [3].

Other areas of a teenager's daily life may also be impaired by the consequences of insufficient sleep. We are just beginning to obtain evidence that moodiness in adolescents is related to sleep patterns. In a recent study of sleep restriction in high school students [36], we asked 13 boys in 9th through 12th grades to reduce their sleep by 2 h a night over 5 consecutive nights. Each evening, they completed a mood checklist (based on the scale of Lubin et al. [37]) as part of a daily sleep/wake/activity diary. The checklist included three scales (positive, negative, depressed). At the end of each week, the students also filled out the Adolescent Depressive Mood Scale of Kandel and Davies [38]. The positive and negative daily mood scales and the weekly Adolescent Depressive Mood Scale all showed significantly dysphoric changes during the period of reduced sleep. Although only a small preliminary study, this finding suggests that a portion of the moodiness of adolescents may be a consequence of insufficient sleep. To the extent that such mood changes interfere with the teenager's ability to cope with daily stresses, poor sleep/wake patterns may represent another serious threat to an adolescent's well-being. Furthermore, chronic mood changes due to chronic insufficient sleep may impair the teenager's relationships with peers and with adults.

Another potentially serious complication of the typical trend for later bedtimes in older adolescents is development of the Delayed Sleep Phase Syndrome (DSPS), which appears to be caused by a defect in the brain's clock mechanism that sets the timing of virtually all of the body's biological functions [39]. In susceptible individuals, this clock can get set incorrectly at a position that causes biological functions (including sleep) to occur later than desired. Retiring and arising at late hours can initiate the appearance of this malfunction. The teenager with DSPS is not necessarily lazy or school phobic or acting out, but is utterly unable to fall asleep before 5:00 or 6:00 a.m. and impossible to wake up before 2:00 or 3:00 in the afternoon. Such a pattern is clearly untenable for a school-aged adolescent and requires special therapy through a sleep disorders center.

Conclusion: Prevention and Intervention

No studies have looked at the possibility that preventive measures can alter patterns of sleep and wakefulness during adolescence. In terms of intervention, there are a few clinical studies in adolescents with DSPS showing successful results of chronotherapy [40, 41]. In terms of insufficient sleep, it is clear that the excessive sleepiness related to insufficient sleep can be eliminated by extending sleep at night [10, 42, 43]. The latter experiments were all conducted in laboratory settings and showed improved physiological alertness and performance with extended sleep. Translation of this approach to the everyday lives of teenagers may be more problematic. Perhaps the most useful approach may be one that combines education of children, parents, teachers, and pediatricians about the fundamental principles of proper sleep hygiene. The first goal of such a program might be to disabuse people about the notion that teenagers need less sleep.

Acknowledgements

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Sleep restriction is not associated with a positive energy balance in adolescent boys[1–3]

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ABSTRACT

Background: A short sleep (SS) duration has been linked to obesity in observational studies. However, experimental evidence of the potential mechanisms of sleep restriction on energy balance is conflicting and, to our knowledge, nonexistent in adolescents.

Objective: We investigated the effects of 3 consecutive nights of partial sleep deprivation on components of energy balance.

Design: In a randomized, crossover design, 21 healthy, normal-weight male adolescents (mean ± SD age: 16.8 ± 1.3 y) completed the following 2 experimental conditions, each for 3 consecutive nights: an SS (4 h/night) and a long sleep (LS; 9 h/night) duration. Endpoints were 24-h energy expenditure (EE), spontaneous physical activity (SPA), postintervention diet-induced thermogenesis (DIT), appetite sensations, ad libitum energy intake (EI), and profiles of plasma ghrelin and leptin.

Results: The 24-h EE on day 3 was 370 ± 496 kJ higher in the SS condition than in the LS condition ($P = 0.003$). This difference in EE was explained by prolonged wakefulness in the SS condition and a 19% higher SPA ($P = 0.003$). In a postintervention breakfast-meal challenge, there was a 0.19-kJ/min smaller incremental AUC in DIT over 4 h in the SS condition than in the LS condition ($P = 0.012$) with no time × condition effect ($P = 0.29$). Subjects consumed 13% less energy in the ad libitum meal in the SS condition ($P = 0.031$), with a concomitant decreased motivation to eat. Concentrations of ghrelin and leptin remained unchanged with sleep restriction.

Conclusion: Short-term sleep restriction in male adolescents is associated with a small negative energy balance driven by increased EE from prolonged wakefulness and a concomitant decreased EI and motivation to eat. This trial was registered at clinicaltrials.gov as NCT01198431. *Am J Clin Nutr* 2012;96:240–8.

INTRODUCTION

A mounting body of observational evidence has revealed that short sleep (SS)[4] duration is associated with weight gain and increased incidence of obesity (1–3), especially in children (4–7). Intervention studies have contributed to our understanding of potential physiologic mechanisms that underpin this association. Spiegel et al (8) were the first to show experimentally that sleep restriction affects the regulation of key appetite hormones (ie, leptin and ghrelin) and appetite sensations in slightly hypocaloric subjects. However, in 3 similar intervention studies, albeit in eucaloric subjects, these observations were not reproduced (9–11), which left the question open as to whether the connection between SS and obesity can be explained by changes in homeostatic consumption behavior. In addition to these proposed physiologic mechanisms that favor an increased drive to eat, staying awake for a longer period of time exposes individuals to the obesogenic environment longer than normal sleepers are exposed, which leads to increased energy intake (EI) (12, 13) and, in particular, increased snacking behavior (10). In summary, an increased EI as a result of partial sleep restriction has not been consistently observed.

Evidence on the effects of sleep restriction on the other side of the energy-balance equation [ie, energy expenditure (EE)] is also conflicting. It has been shown that partial sleep deprivation does not influence 24-h EE (10, 11). This also seemed to be the case when the resting metabolic rate was investigated separately (14). However, divergent findings have also been reported, after both total sleep deprivation (15) and partial sleep deprivation (16). Conflicting results have also been observed regarding the effect of sleep restriction on physical activity levels and patterns (9, 11, 12, 14) that could influence total EE.

Because of these conflicting results and the fact that these investigations have, to our knowledge, been conducted only in adults, we aimed to investigate the effects of 3 consecutive nights of partial sleep deprivation on components of energy balance in a homogenous group of healthy teenage boys. This age group is particularly interesting because it has been observed that adolescents have experienced important declines in their sleeping time over the past decades (17), and they have an irregular sleep-wake cycle (18), which thereby constitutes a potential group at risk of developing

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[2] This study is part of the Optimal well-being, development and health for Danish children through a healthy New Nordic Diet (OPUS) project. The OPUS project (The OPUS Centre, Department of Human Nutrition, Faculty of Life Sciences, University of Copenhagen) is supported by a grant from the Nordea Foundation.

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[4] Abbreviations used: BMR, basal metabolic rate; DIT, diet-induced thermogenesis; EE, energy expenditure; EI, energy intake; KSS, Karolinska Sleepiness Scale; LS, long sleep; RQ, respiratory quotient; SPA, spontaneous physical activity; SS, short sleep; VAS, visual analog scale.

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obesity. We hypothesized that 3 consecutive nights of only 4 h in bed would be accompanied by increased appetite sensations and an increased spontaneous food intake without affecting the total EE.

SUBJECTS AND METHODS

Subjects

Twenty-one healthy, normal-weight [age-adjusted BMI (in kg/m^2) <25 on the basis of Cole et al (19)] male adolescents between 15 and 19 y of age were recruited for the study through advertisements and by word of mouth. Volunteers were excluded from participation for any of the following reasons: smoking, unstable body weight (±3 kg) during the 6 mo before testing, regular physical exercise (>3 h/wk), excessive intake of alcohol (>7 drinks/wk), substance abuse, excessive intake of caffeine (>300 mg/d), metabolic disease (eg, thyroid disease, heart disease, or diabetes), medication use that could interfere with the outcome variables, eating disorder, highly restrained eating behavior (score ≥10 for cognitive dietary restraint on the Three-Factor Eating Questionnaire), irregular eating pattern (eg, skipping breakfast), self-reported sleep problems (score >5 on the Pittsburgh Sleep Quality Index), transmeridian travel in the past month, and inability to comply with the protocol. All subjects (or parents of subjects aged <18 y) gave written informed consent to participate in this study, which had received approval from the ethical committee of the Capital Region of Denmark. Volunteers participated in the following 4 visits: an information meeting [ie, a preliminary visit aimed at informing subjects (and parents for subjects <18 y) about the procedures and protocol requirements], a screening visit to evaluate inclusion and exclusion criteria, and two 4-d experimental conditions.

Study design and procedure

A schematic overview of the study protocol is shown in **Figure 1**. With the use of a within-subject experimental design, each participant was engaged, in a random order, in each of the 2 following conditions: *1*) SS (4 h/night from 0300 to 0700 for 3 consecutive nights) and *2*) long sleep (LS; 9 h/night from 2200 to 0700 for 3 consecutive nights). These 2 experimental conditions were randomly assigned by using a computerized randomization scheme and separated by 3–4 wk. Between experimental conditions, participants were asked to maintain normal activities and, particularly, not to change sleeping, eating, or physical activity patterns. Vigorous physical activity was not allowed 24-h before testing, and a normal sleep schedule had to be respected for 3 d before testing. Subjects were required to arrive at the University of Copenhagen research laboratory in a fasting state, and all subjects were in good health on test days. Body weight was measured every morning on a calibrated scale (Lindell Tronic 8000; Samhall Lavi) with subjects in a fasting state with an empty bladder and wearing light clothes and without shoes. Likewise, subject temperature was measured in the ear canal with a thermometer (Braun ThermoScan; Braun GmbH) on awakening each morning.

The 3 nights were spent in a whole-body calorimetric chamber. During the 2 initial nights, the chamber door was open so that subjects could become accustomed to the environment. On the morning after the second night, the chamber door was sealed, and the subjects spent 24 h in the chamber for measurements of EE. Subjects had access to a computer with Internet, a telephone, and a television with a DVD player during the stay. The following time schedule was followed during the 24-h stay in the chamber: door closed at 0830, breakfast at 0900, 15 min of cycling at a constant resistance (75 W) and cadence (50 rpm) at 1000 and again at 1600, lunch at 1300, a short period of standardized light walking (25 rounds in the chamber, which corresponded to ~5 min) at 1130 and again at 1430, snack at 1530, dinner at 1800, snack at 2100, lights off at 2200 (for LS) or 0300 (for SS), awaken at 0700, basal metabolic rate (BMR) measurements at 0730, and chamber exit at 0830. Trained personnel regularly visually monitored subjects to ensure their safety and compliance to the protocol (eg, by making contact at any sign of sleeping during waking hours and BMR measurements).

Diet

The basal energy requirement was individually calculated by using the WHO formula (20) for this age group

$$[0.068 \times \text{weight (in kg)} + 0.57 \times \text{height (in m)} + 2.16 \times \text{physical activity factor (1.4 for chamber condition; 1.6 for free-living condition)} \quad (1)$$

EI was distributed as 25% from breakfast, 30% from lunch, 30% from dinner, and 15% from snacks. The macronutrient composition

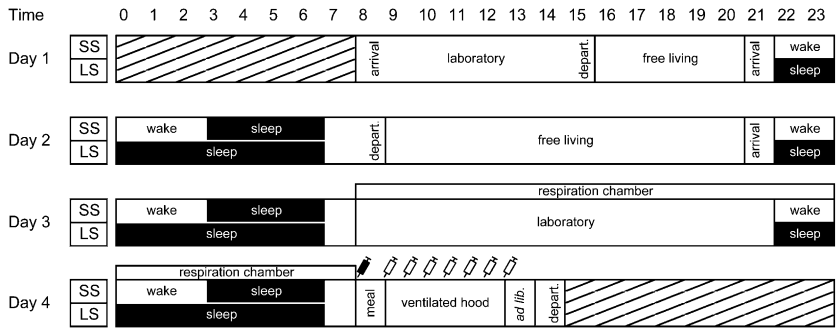

FIGURE 1. Study outline. Hatched areas represent time periods outside the study protocol. Participants spent both sleeping and wake time in the respiration chamber on days 1 and 2 to become accustomed to the chamber. Syringe symbols denote blood samplings (filled syringe denotes a fasting sample). Visual analog scales were provided at the same time points as blood sampling. Meals were given at the same time points in both conditions as follows: breakfast at 0900, lunch at 1300, snack at 1530, dinner at 1800, and snack at 2100. Meals outside of the laboratory were provided by our research kitchen staff. In free-living periods, participants were encouraged to engage in everyday activities but to abstain from scheduled physical activity. *ad lib.*, ad libitum meal test; arrival, arrival at the laboratory; depart., departure from the laboratory; laboratory, period during which participants stayed at the laboratory; LS, long-sleep condition (9 h from 2200 to 0700); meal, breakfast meal; SS, short-sleep condition (4 h from 0300 to 0700); ventilated hood, repeated ventilated hood measurements.

was, on average for the whole day, 10% of energy from protein, 30% of energy from fat, and 60% of energy from carbohydrates. Dietary calculations were made by using the food database from the Danish National Food Agency (version 6.0, 2005; Technical University of Denmark). Calculations were done with Dankost 3000 software (version 7.01, 2009; Dankost). All meals consisted of everyday products and were prepared in the research kitchen of the laboratory. Meals were given at the same time points in both conditions. Meals outside of the laboratory were provided to participants as ready-made meals with a written instruction on heating and handling. A text-message system was set up to remind participants to eat at the designated times. Participants were encouraged to eat the whole serving at each meal. Any leftovers were recorded, and the actual energy of that particular meal was recalculated. Water was offered ad libitum.

Sleep recordings and evaluation

Surface electrodes for electroencephalography, electrooculography, submental electromyography, and electrocardiography measurements were fitted on subjects by using a portable polysomnographic device (TrackitTM; Lifelines Neurodiagnostic Systems Inc) before they left the metabolic laboratory on the first day. Each morning, the electrodes were checked for signal strength and impedance. Post hoc analyses of sleep length were done by using visual scoring and were conducted by the same trained researcher for all recordings.

Each morning, at the same time point during both experimental conditions, subjective sleepiness was evaluated by using the Karolinska Sleepiness Scale (KSS) (21). The KSS consists of a question on subjective sleepiness with a 10-point scale with a phrase associated to each point that ranged from "1: extremely alert" to "10: extremely sleepy–can't keep awake." The KSS has been shown to be highly correlated with brain activity (α and θ activity) (21) and is a useful proxy behavioral indicator of sleepiness (22).

Measurement of EE

After a run-in period of 2 nights, the EE and respiratory quotient (RQ) were measured in one of 2 duplicate respiratory chamber calorimeters of the Department of Human Nutrition (23). The same chamber was used on both occasions for any subject. Gas exchange in the chamber was calculated from the measured airflow and concentrations of oxygen and carbon dioxide at the outlet of the chamber as well as in the fresh air going in. We performed a 24-h urine collection to determine nitrogen excretion. EE was calculated, including data on nitrogen excretion, on the basis of equations by Elia and Livesey (24). On the fourth day, subjects were awakened at 0700 but were instructed to remain lying still in bed, apart from getting up for voiding if needed. The registration of respiratory gas exchange between 0730 and 0830 was used for assessment of the BMR.

After subjects left the chamber, measurements of diet-induced thermogenesis (DIT) and RQ were performed before and for 3 h after a standardized breakfast that consisted of 25% of the individual daily energy requirement and with an energy distribution of 11% of energy protein, 27% of energy fat, and 62% of energy carbohydrate by using a ventilated hood system (Jaeger Oxycon Pro; Cardinal Health Care GmbH) as described in detail elsewhere (25). The duration of each measurement was 25 min where the first 5 min of each 25-min measurement was omitted. EE was calculated by using a formula assuming a fixed protein catabolism (26). The accuracy of the ventilated hood was validated by using an alcohol-burning test on a weekly basis with a CV of 1.5%.

Physical activity

Spontaneous physical activity (SPA) in the respiration chamber was assessed by using 2 microwave radar detectors (Sisor Mini-Radar; Statistic Input System SA). The radar detected when the subject was moving, and the generated signal was received by the transceiver and electronically stored for later analyses. SPA measurements indicated the percentage of time when the subject was moving.

Measurement of ad libitum EI

To measure spontaneous EI in an experimental context, participants were offered an ad libitum lunch at 1300 on day 4. The ad libitum meal was a semihomogenized spaghetti bolognese meal (961 kJ/100 g; 15% of energy protein, 30% of energy fat, and 55% of energy carbohydrate) and 200 mL tap water. Subjects were instructed to eat at a constant pace and to stop eating when they felt satiated. Subjects had a maximum of 30 min to consume the meal, and the serving of pasta was substantially larger than the expected intake (8 MJ offered). The meal was weighed before lunch, and the uneaten portion was weighed after lunch. Ad libitum EI was assessed by a food technician by using calculations performed on the amount of the meal consumed. The ad libitum test meal has been shown to be reproducible in our laboratory (27).

Measurement of appetite

Participants rated their sensations of hunger, satiety, prospective food consumption, fullness, and desire to eat meat, fish, something sweet, something salty, or something rich in fat on a visual analog scale (VAS) at different time points around the standardized breakfast on day 4. The VAS method has been described in detail and was shown to be both reproducible and valid for measuring appetite sensations in our laboratory (28). Assessments were completed before and immediately after the breakfast test meal and subsequently at every 30 min until the ad libitum lunch meal. In addition, the VAS was filled out every hour for a 4-h period after the ad libitum lunch.

Biochemical analyses

Blood samples were drawn through an indwelling superficial forearm venous catheter in the fasting state and every 30 min during the DIT measurement (a total of 8 time points). The sampling was done under standardized laboratory conditions. Samples were drawn into heparinized tubes, centrifuged, separated into aliquots, and frozen at -80°C until analyzed. Samples from each subject were analyzed continually in a single batch to eliminate assay variation. Blood samples were analyzed for total plasma ghrelin [determined by using an enzyme-linked immunosorbent assay (Millipore)], total plasma leptin [determined by using a radioimmunoassay (Millipore)], and free triiodothyronine, thyroxine, and thyroid-stimulating hormone [determined by using a solid-phase, enzyme-labeled chemiluminescent immunometric assay (Siemens Immulite 1000; Siemens Medical Solutions)].

Questionnaires

Three questionnaires were administered during the preliminary visit to better characterize participants. The 51-item Three-Factor Eating Questionnaire (29) was used to assess 3 factors related to cognition and eating behaviors: cognitive dietary restraint (intent to control food intake), disinhibition (overconsumption of food in response to cognitive or emotional cues), and susceptibility to hunger (food intake in response to feelings and perceptions of hunger). This questionnaire has been validated, and its 3 scales have been reported to show good test-retest reliability (29, 30). In addition, each participant completed the Pittsburgh Sleep Quality Index (31), which is a self-rated questionnaire that assesses sleep quality and disturbances over the preceding month. A total score >5 was associated with poor sleep. Finally, the Cohen's Perceived Stress Scale (32) was completed to evaluate the level of stress in the everyday lives of participants. This questionnaire contained 10 questions, and a score of <10 indicated good management of stress.

Statistical analysis

The power-calculation analysis performed before the beginning of the study showed that data from 20 subjects gave a power of 90%, which was sufficient to detect a difference in 24-h EE between sleep protocols of 2% (SD: ±2%) with an $\alpha = 0.05$. Before statistical analyses were conducted, all continuous variables were tested for normality and homogeneity of variance by using visual inspection of both quantile-quantile plots and plots of residuals against fitted values. A Box-Cox calculation was conducted, and the necessary transformations were done to ensure normality and homogeneity of variance. Differences in EE (respiration chamber), EI (ad libitum), AUC, and area over the curve (trapezoidal rule) and between SS and LS in fasting concentrations of hormones were analyzed by using a multiple linear regression model with robust estimation of variance (Huber-White estimation model) with the order of treatment as a fixed explanatory variable. Differences in repeated measurements of EE (hood), the VAS, and appetite-regulating hormones were tested by using a random coefficient model with maximum-likelihood estimation. Each model was tested for a correlation pattern, and the model was fitted as either unstructured or with an exponential correlation structure based on Akaike's criteria. The time × condition effect in the random coefficient model was tested against a simpler model by using a likelihood ratio test. The order of intervention was a fixed explanatory variable. For statistical evaluation, Stata software (version 11; StataCorp) was used. Data are presented as means ± SDs unless otherwise specified. $P < 0.05$ was considered significant.

RESULTS

Participant characteristics and sleep data

Descriptive characteristics of subjects are shown in **Table 1**. None of the subjects were restrained eaters, and they all had low scores of disinhibition and susceptibility to hunger. In addition, subjects had a fairly good sleep quality in general as well as a normal perceived stress in their everyday lives.

Fasting morning weight did not change over the course of the 4-d intervention in either condition (random coefficient model), and there were not any differences in fasting weight on day 4 between conditions (paired sample *t* test).

TABLE 1
Subject characteristics[1]

Variables	Values (n = 21)
Age (y)	16.8 ± 1.3
Body weight (kg)	65.7 ± 5.8
BMI (kg/m^2)	21.0 ± 1.8
Waist circumference (cm)	74.9 ± 4.5
Energy intake inside the chamber (MJ)	10.7 ± 0.6
Energy intake outside the chamber (MJ)	12.3 ± 0.7
Pittsburgh Sleep Quality Index score	3.86 ± 2.17
Three-Factor Eating Questionnaire	
Cognitive dietary restraint	4.73 ± 3.22
Disinhibition	4.36 ± 2.13
Susceptibility to hunger	4.55 ± 3.10
Cohen's Perceived Stress Scale score	8.68 ± 4.20

[1] All values are means ± SDs.

Data from polysomnography recordings showed that participants slept, on average, 506 ± 42 and 243 ± 15 min during the LS and SS conditions, respectively. Values for the KSS questionnaire went from 4.7 ± 1.7 (day 1) to 7.8 ± 0.9 (day 4) in the SS condition and from 5.2 ± 1.6 (day 1) to 4.1 ± 1.6 (day 4) in the LS condition. There was a significant time × condition effect ($P = 0.012$) with a significantly higher KSS score in SS compared with LS conditions on days 2, 3, and 4 ($P < 0.001$ for all days).

Measures of EE

Twenty-four–hour EEs in the respiration chamber were 10,469 ± 885 kJ and 10,099 ± 766 kJ for the SS and LS conditions, respectively ($P = 0.003$). These values corresponded to a 370 ± 496-kJ higher daily EE in the SS condition than in the LS condition (**Figure 2**). The profile of 24-h EE from the respiration chamber showed that the difference in 24-h EE originated from the difference in EE during the habitual nighttime period [6.8 ± 0.7 kJ/min (SS) compared with 5.3 ± 0.4 kJ/min (LS); $P < 0.001$) (**Figure 3**). There was no difference between conditions in either daytime EE [8.2 ± 0.7 kJ/min (SS) compared with 8.3 ± 0.7 kJ/min (LS); $P = 0.42$], sleeping EE [4.9 ± 0.5 kJ/min (SS) compared with 4.9 ± 0.4 kJ/min (LS); $P = 0.54$], or BMR [5.8 ± 0.6 kJ/min (SS) compared with 6.0 ± 0.7 kJ/min (LS); $P = 0.082$] (Figure 2). SPA followed the same pattern with a significantly higher SPA during habitual nighttime in the SS condition than in the LS condition [16 ± 7% (SS) compared with 3 ± 1% (LS); $P < 0.001$], which explained the 19% higher SPA over 24 h [16 ± 5% (SS) compared with 13 ± 5% (LS); $P = 0.003$; Figure 2]. The 24-h RQ value was significantly lower in the SS condition than in the LS condition [0.88 ± 0.02 (SS) compared with 0.89 ± 0.02 (LS); $P = 0.022$]. This difference in RQ was shown during sleep [0.88 ± 0.03 (SS) compared with 0.85 ± 0.03 (LS); $P < 0.001$] and BMR measurement [0.88 ± 0.04 (SS) compared with 0.85 ± 0.04 (LS); $P = 0.049$] (Figure 2).

DIT after the standardized breakfast meal challenge is shown in **Figure 4**. There was no significant time × condition effect for DIT (P-interaction = 0.29). However, there was a 0.19-kJ · min (29%) larger incremental AUC (baseline-subtracted AUC) in the LS condition than in the SS condition [0.67 ± 0.058 kJ · min (SS) compared with 0.86 ± 0.058 kJ · min (LS); $P = 0.012$]

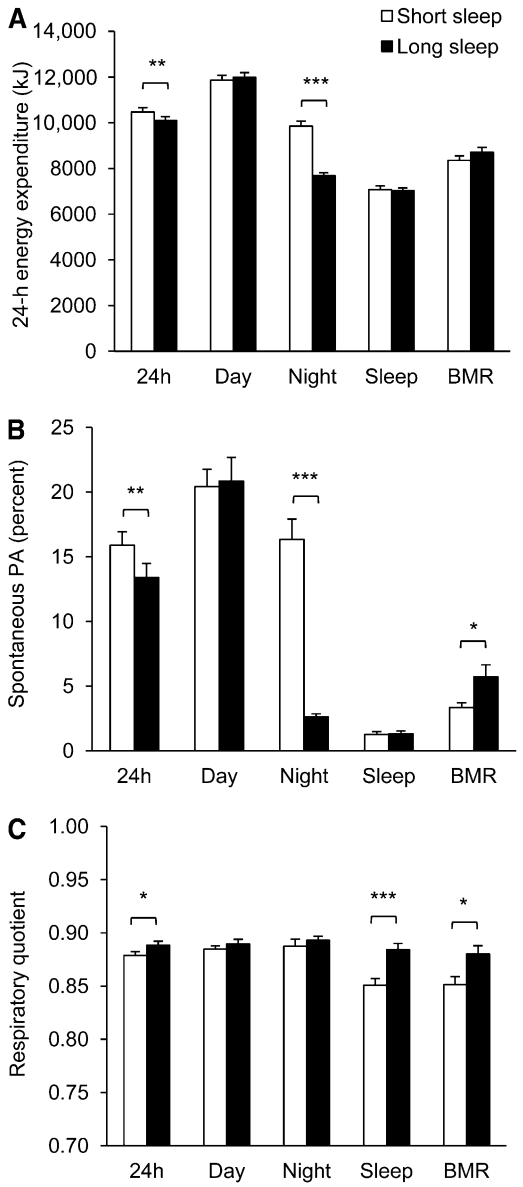

FIGURE 2. Calorimetric chamber data (±SEMs): data on energy expenditure (A), spontaneous physical activity (B), and respiratory quotient (C) from the 24-h stay in the respiration chamber. Time periods on the *x* axis are 24 h from 0830 to 0830 (next day). Open bars represent the short-sleep condition, and filled bars represent the long-sleep condition. Error bars represent SEMs. *,**,***Significantly different between conditions (Huber-White estimation model with the order of intervention as an explanatory variable; $n = 21$): $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. BMR, period for measurement of the basal metabolic rates (0730–0830); Day, daytime period (0830–2200); Night, sleep-wake period (2200–0300; subjects slept in the long-sleep condition and were awake in the short-sleep condition); PA, physical activity; Sleep, sleeping period for both conditions (0300–0730).

(Figure 4). Two subjects were excluded from this analysis because of a missing value for the first postprandial measurement ($t = 60$ min).

Measures of temperature and thyroid hormones

The morning temperature was not different on day 1 [36.4°C (SS) compared with 36.3°C (LS); $P = 0.21$] or day 4 [36.1°C (SS) compared with 36.3°C (LS); $P = 0.35$]. Differences in temperature between days 1 and 4 were −0.30°C and 0.00°C for SS and LS conditions, respectively ($P = 0.075$). There was no time × condition effect (P-interaction = 0.72). Measures of thyroid hormones showed a significant difference in free triiodothyronine between conditions on the morning of day 4 [4.91 pmol/L (SS) compared with 4.34 pmol/L (LS); $P < 0.001$] but not in thyroxine [1.12 ng/dL (SS) compared with 1.10 ng/dL (LS); $P = 0.26$] or thyroid-stimulating hormone [1.76 mIU/L (SS) compared with 1.85 mIU/L (LS); $P = 0.34$].

Measures of appetite, EI, and appetite hormones

Profiles of subjective appetite (VAS scores for hunger, satiety, fullness, and prospective food intake) in response to the standardized breakfast on day 4 are presented in **Figure 5**. All of these VAS scores were affected toward a decreased motivation to eat in the SS condition. Thus, there was a significantly larger AUC or area over the curve for satiety, fullness, hunger, and prospective food intake ($P = 0.004$, $P = 0.003$, $P = 0.049$, and $P = 0.013$, respectively) (**Figure 6**). In the random coefficient model, there was a time × condition effect for prospective food intake ($P = 0.028$), whereas no effects were shown for fullness ($P = 0.20$), hunger ($P = 0.28$), and satiety ($P = 0.20$). Fasting values did not differ between conditions. There was a significantly larger AUC in the SS condition for the desire to eat meat and fish ($P = 0.048$) and something sweet ($P = 0.019$) but not for thirst ($P = 0.42$). There was a tendency toward an increased desire to eat something rich in fat ($P = 0.063$) and salty ($P = 0.064$). There was no time × condition effect in the random coefficient model for any of the scores ($P = 0.36$, $P = 0.25$, $P = 0.23$, $P = 0.39$, and $P = 0.64$ for fat, meat, salt, sweet, and thirst, respectively).

Data on the ad libitum EI assessment are presented in **Table 2**. Subjects consumed 13% less in the SS condition than in the LS condition ($P = 0.031$). The average eating time (min) and eating rate (kJ/min) were not different between conditions.

Plasma concentrations of leptin and ghrelin are presented in **Figure 7**. Neither ghrelin nor leptin concentrations differed between conditions. In the leptin analyses, 3 subjects were excluded because of fasting concentrations >12 μg/L, which was considered above the normal range for this group of subjects. However, the significance of results did not change keeping these subjects in our analyses.

DISCUSSION

For the first time to our knowledge, the current study examined whether short-term sleep restriction affects components of energy balance in adolescents. Taken together, our data provided evidence that 3 consecutive nights of 4 compared with 9 h of sleep per night were associated with increased EE derived from increased wakefulness. Contrary to our hypothesis, we also observed a decreased EI after SS at a subsequent ad libitum test meal. This finding was accompanied by a decreased motivation to eat.

EE

The increased 24-h EE during the SS condition in our teenagers was not in line with our hypothesis and contradicted previous findings (10, 14, 16). However, in studies by Nedeltcheva et al (10, 16), the doubly labeled water technique was used to measure EE.

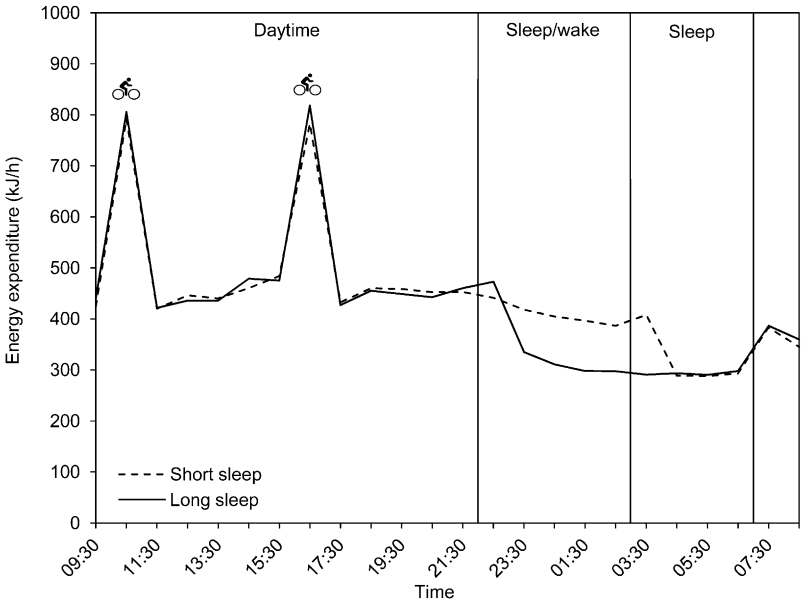

FIGURE 3. Energy-expenditure profile from the calorimetric chamber: profile of the 24-h energy expenditure between sleep conditions (n = 21). The cycle icon represents the time of standardized cycling at a constant resistance (75 W) and cadence (50 rpm) on an ergometer cycle.

We used whole room calorimetry, which is able to detect even small changes in EE not picked up by the doubly labeled water technique (33). The increase in 24-h EE in our study was solely due to an increased EE during the time period in which subjects were awake in the SS condition and asleep in the LS condition. The extra energy spent during this period (from 2200 to 0300) constituted 98% of the total difference in 24-h EE. This effect has previously been reported by Jung et al (34), whose study supported our finding of a sleep-wake–related difference in EE. In addition, this observation was substantiated because BMR did not differ between conditions. An unchanged resting metabolic rate after sleep restriction has also been reported previously in different groups of subjects (10, 11, 14), whereas other studies have described a drop in resting metabolic rate after sleep restriction by using different methodologies (15, 16).

An increased thyroid activity has been reported previously after partial sleep restriction (11). Because we did not observe an increase in EE during either sleep or BMR, a possible effect of thyroxine 3 on EE in our teenagers was negligible. Previous studies have shown decreased body temperatures after total sleep restriction in both humans (35, 36) and rats (37), which could offer an explanation of increased thyroid activity. However, we showed a tendency toward a decreased body temperature only after SS in our study. Thus, the cause of elevated thyroxine 3 concentrations remains elusive.

Activity-related thermogenesis is probably a more obvious explanation of the increased EE. We showed that the increased nighttime SPA explained the increased 24-h SPA in the SS condition with no difference in either daytime or sleeping SPA between conditions (Figure 2). Previous studies have shown that both the amount and intensity of physical activity during free-living conditions after only one night of sleep curtailment can be suppressed (9), but opposite findings have also been reported by using both similar sleep-restriction protocols (12) as well as total sleep deprivation (14). In the current study, SPA in the respiration chamber was significantly increased in the SS condition because of the longer period of time spent awake. Although participants had access to recreational media, it is likely that the increased movement in the SS condition was a result of an increased effort to stay awake. However, physical activity in the respiration chamber was very limited because of the confinement and was by no means comparable to real-life conditions. Thus, caution must be exercised with regard to the clinical significance of these SPA data obtained in the respiration chamber.

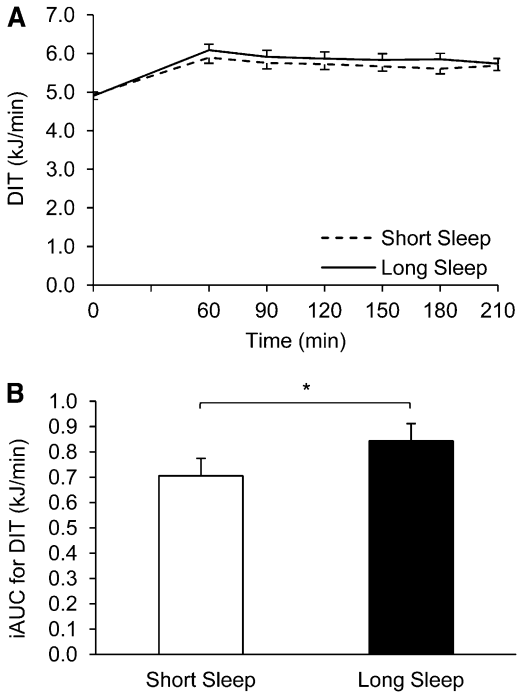

FIGURE 4. DIT data (±SEMs): DIT before and after the standardized meal challenge (A) and iAUC (trapezoid rule) calculations (B). Error bars represent SEMs. No statistically significant time × condition effect was shown in the random coefficient model (P-interaction = 0.29; n = 19). *Significantly different between conditions, $P < 0.05$ (Huber-White estimation model with the order of intervention as an explanatory variable; n = 19). DIT, diet-induced thermogenesis; iAUC, incremental AUC.

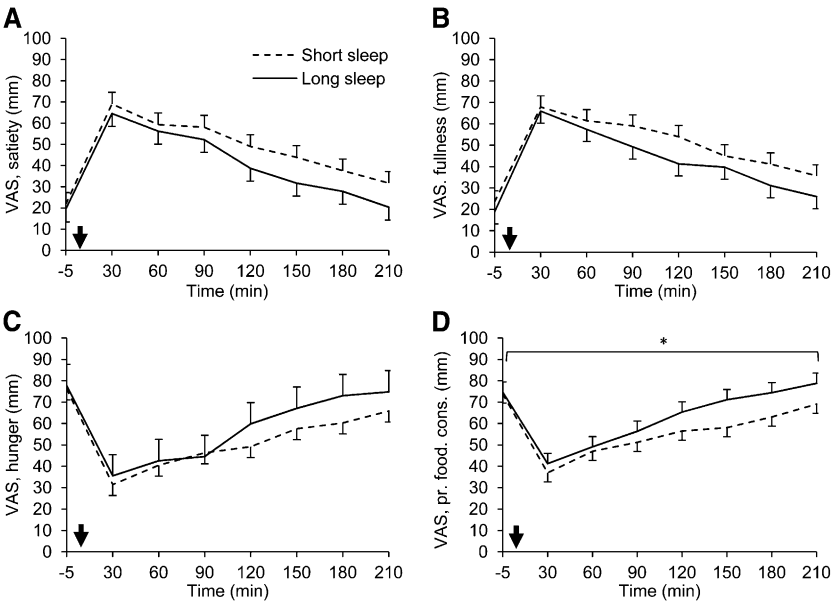

FIGURE 5. Appetite sensations: profiles of VAS scores (±SEMs) (before and after the standardized breakfast meal challenge for satiety (A), fullness (B), hunger (C), and prospective food consumption (D). No significant time × condition effect for fullness, hunger, or satiety was shown. There was a significant time × condition effect for prospective food consumption ($P < 0.05$; $n = 21$; random coefficient model). The black arrow on the x axis denotes the time of the meal challenge. Error bars represent SEMs. *Significantly different between conditions ($P < 0.05$; $n = 21$; random coefficient model). pr. food. cons., prospective food consumption; VAS, visual analog scale.

DIT normally accounts for ~10% of 24-h EE when subjects are in energy balance, but changes in postprandial metabolism can give insight into a potential functional role of sleep in relation to long-term energy balance. After a standardized breakfast meal, we showed a small but significant difference in DIT calculated as incremental AUC over 4 h. On average, DIT was 40.1 ± 14.0 kJ lower in the SS condition than in the LS condition for the 4-h period. This result was contrary to results from recent studies (10, 16) in which no difference in DIT have been reported. However, another recent study showed a transient decrease (20%) in DIT after only one night of total sleep deprivation, which suggested a sleep-related change in metabolism (15). However, a comparison between the 2 studies was hampered because the 2 sleep protocols were very different, and a physiologically different response to total sleep deprivation and partial sleep deprivation has been proposed (38).

The observed decrease in RQ during both sleep and BMR suggested that sleep restriction was accompanied by a change in substrate use. However, we suggest that this difference was merely a consequence of the temporal difference in energy balance that stemmed from prolonged wakefulness in the SS condition and, thus, was not an intrinsic change in mobilization or breakdown of substrates after SS.

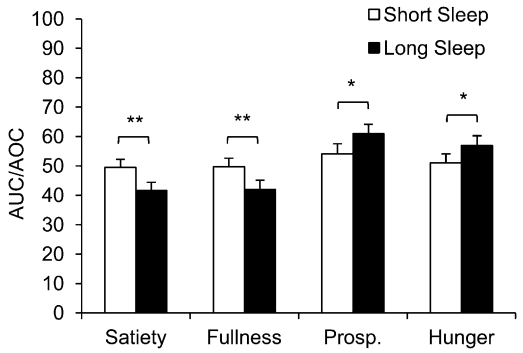

FIGURE 6. AUC/AOC for visual analog scales on appetite. Means (±SEMs) of AUC (trapezoid rule) (satiety and fullness) and AOC (trapezoid rule) (hunger and prospective food intake) before and after the standardized breakfast meal challenge on day 4 are shown. *·** Significantly different between conditions (Huber-White estimation model with the order of condition as an explanatory variable): *$P < 0.05$, **$P < 0.01$. AOC, area over the curve; Prosp., prospective food intake.

EI

In contrast to our hypothesis, we showed that the ad libitum food intake, which is a proxy for spontaneous EI, and subjective motivation to eat were reduced after 3 nights of sleep curtailment. To our knowledge, this is a new finding and is in contrast to previous findings in which both increased food intake (11–13) and unchanged food intake (9, 10) have been reported. However, there was a large interindividual variation in the difference in ad libitum food intake between conditions, and in addition, 7 of 21 subjects actually had an elevated EI in the SS

TABLE 2
Energy intake from the ad libitum lunch meal[1]

	Short sleep	Long sleep	P^2
Energy intake (kJ)	3430.3 ± 1166.9	3883.6 ± 1341.2	0.031
Duration (min)	9.8 ± 3.3	10.6 ± 3.7	0.27
Eating rate (kJ/min)	354.9 ± 107.9	376.1 ± 92.5	0.23

[1] All values are means ± SDs. Energy intake, duration of the meal, and eating rate are from the ad libitum meal test.

[2] P values are for the difference between sleep conditions (Huber-White estimation model with the order of sleep condition as an explanatory variable; $n = 21$).

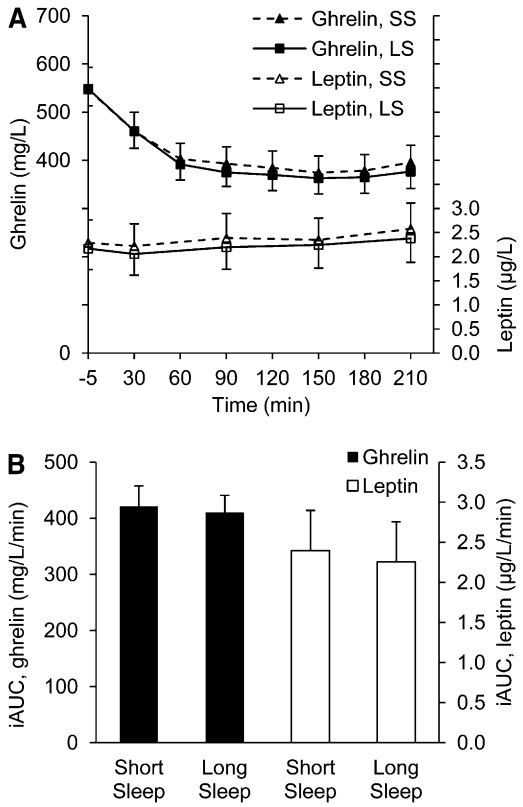

FIGURE 7. Plasma concentrations (±SEMs) of ghrelin and leptin before and after the standardized meal challenge (A) and iAUC (trapezoid rule) calculations (B). Dotted lines in panel A represent the short-sleep condition, and solid lines represent the long-sleep condition. Error bars represent SEMs. There was no statistically significant time × condition effect in the random coefficient model [$P = 0.31$ ($n = 20$) and $P = 0.32$ ($n = 17$) for the transformed time × condition effect for ghrelin and leptin, respectively]. There was no statistical difference in iAUC between conditions [$P = 0.50$ ($n = 20$) and $P = 0.41$ ($n = 17$) for the transformed value for ghrelin and leptin, respectively]. iAUC, incremental AUC.

condition. To our knowledge, the use of an ad libitum setting has not been validated in teenagers, and on the basis of the current study, it seems that the group displays a considerable degree of heterogeneity.

Despite the large variation in food intake as a result of sleep restriction, the significant difference in ad libitum food intake was supported by data of appetite sensations. Indeed, the drive to eat was lower in the SS condition. However, there was no significant correlation between individual differences in food intakes and VAS scores (data not shown). This further raised the question as to whether the ad libitum meal settings and VAS scores are indeed a valid proxy for EI and appetite sensations in adolescents.

In the current study, we could not rule out the fact that the teenagers might have displayed compensatory eating behaviors after the study. Food intakes were highly controlled during the study until the ad libitum meal setting at lunch on day 4. It has previously been described that going to bed late is associated with late eating behavior, and this combination is associated with increased BMI (18). We continued to assess appetite sensations only until 1800 on day 4 and showed no difference between conditions during this period (data not shown). However, we did not assess compensatory eating behaviors in the afternoon or evening on day 4. This lack of assessment is a limitation of the study. A longer follow-up period is recommended in future studies to adequately capture potential compensations in energy balance after the intervention.

Increased ghrelin and decreased leptin concentrations have previously been associated with sleep restriction, and several studies have addressed this modulation of neuroendocrine regulation of appetite (8–11, 16, 39–44). We did not find support for an endocrine explanation to the decreased food intakes in our teenagers inasmuch as neither ghrelin nor leptin concentrations differed between conditions. However, the measurement of 24-h profiles of ghrelin and leptin could have provided a more robust conclusion in the current study. Although this lack of measurement was a methodologic limitation of the study, for ethical reasons, we were not able to collect blood during 24 h. The fact that we did not see any changes in leptin and ghrelin is in line with previous observations whereby the wakeup time was the same in both conditions (9, 10). This methodologic difference between studies (delay or difference between time of blood sampling and time of wake-up) made it difficult to compare results. Therefore, whether appetite regulation is acutely affected by restricted sleep can be questioned. Whether longer periods of sleep restriction have a more permanent influence on ghrelin and leptin concentrations as indicated in observational studies has, to our knowledge, not been investigated in intervention studies.

In conclusion, we showed that acute sleep restriction was associated with increased 24-h EE in adolescent boys as a consequence of prolonged wakefulness. Moreover, we observed that the motivation to eat and subsequent spontaneous EI, in contrast to what has previously been shown, decreased after SS. In this study, sleep restriction in male teenagers was associated with a small negative energy balance. Future studies should put efforts into better understanding the link between SS duration and energy balance in younger age groups over a longer period of time.

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The authors' responsibilities were as follows—LK, J-PC, UH, PJ, and AS: analyzed the data; LK: conducted the research, wrote the manuscript, and had primary responsibility for the final content of the manuscript; and all authors: designed the research and read and approved the final manuscript. The funding organization played no role in the design, implementation, analysis, or interpretation of data. None of the authors had a conflict of interest.

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