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SLEEP

Uncovering Residual Effects of Chronic Sleep Loss on Human Performance

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Sleep loss leads to profound performance decrements. Yet many individuals believe they adapt to chronic sleep loss or that recovery requires only a single extended sleep episode. To evaluate this, we designed a protocol whereby the durations of sleep and wake episodes were increased to 10 and 32.85 hours, respectively, to yield a reduced sleep-to-wake ratio of 1:3.3. These sleep and wake episodes were distributed across all circadian phases, enabling measurement of the effects of acute and chronic sleep loss at different times of the circadian day and night. Despite recurrent acute and substantial chronic sleep loss, 10-hour sleep opportunities consistently restored vigilance task performance during the first several hours of wakefulness. However, chronic sleep loss markedly increased the rate of deterioration in performance across wakefulness, particularly during the circadian "night." Thus, extended wake during the circadian night reveals the cumulative detrimental effects of chronic sleep loss on performance, with potential adverse health and safety consequences.

INTRODUCTION

The capacity to sustain alertness and attention is essential for survival, yet it is a finite resource that progressively declines over consecutive hours awake. Homeostatic physiologic processes that occur during sleep replenish this capacity, but how much sleep is required for satisfactory alertness and performance continues to be debated. There are two types of sleep loss: acute sleep loss consisting of one continuous extended wake episode, and chronic sleep loss consisting of insufficient sleep over multiple days. A parsimonious account of sleep homeostasis is that the degree of impairment reflects the accumulation of excess wakefulness independent of whether the accumulation occurs acutely or chronically (*1*). However, recent animal data suggest that acute and chronic sleep loss have distinct homeostatic mechanisms. Understanding the fundamental properties of the sleep homeostatic regulation of alertness and performance in humans has both public health relevance for occupational policy and therapeutic implications for the discovery of novel wake-promoting therapies.

An important experimental limitation in studying the homeostatic regulation of performance based on the previous sleep-wake history is the confounding influence of circadian rhythms. Endogenous circadian rhythms are coordinated by pacemaker activity of the suprachiasmatic nucleus (SCN) of the hypothalamus (*2*). The circadian system promotes wakefulness and performance during the circadian day; this alerting signal dissipates during the circadian night, at which time the circadian pacemaker promotes sleep (*3*). However, acute sleep loss can directly influence neural activity in the SCN (*4*), and the amplitude of the circadian oscillation in performance increases with longer consecutive hours awake (*5*–*8*). As a result of these nonlinear interactions, the circadian influence on performance during acute sleep loss is small early in a waking bout, but after many consecutive hours awake, performance and alertness become increasingly dependent on the circadian phase. In previous chronic sleep loss protocols, waking performance was only assessed at restricted combinations of homeostatic pressure and circadian phase. It is necessary to account for the confounding influence of circadian phase by distributing the sleep-wake schedule across the full circadian cycle to determine fundamental properties of sleep homeostasis.

We designed a protocol to separate the influences of chronic sleep loss, long consecutive hours awake, and circadian timing on a task of sustained attention. The protocol used a forced desynchrony (FD) paradigm, which allows the circadian pacemaker to cycle at its endogenous period [~24.2 hours in humans (*9*)] independent from the experimental sleep-wake schedule. The FD protocol lasted 21 calendar days, consisting of 12 sleep-wake cycles of 42.85 hours, each with 32.85 hours of scheduled wakefulness and 10 hours of scheduled sleep. This wake duration is similar to that of a resident physician working a 30-hour "on call" shift or others who work through the night and into the next day. The reduced sleep-to-wake ratio of 1:3.3 during FD, which is comparable to 5.6 hours of sleep every 24 hours, imposed chronic sleep loss across the 3 weeks on the FD protocol in addition to the acute sleep loss from the long consecutive hours awake within each 42.85-hour FD cycle. The FD protocol began under entrained conditions, with a normal phase relation between the circadian and scheduled sleep-wake cycles. The differential length between the 42.85-hour sleep-wake cycle and the near–24-hour circadian cycle caused uncoupling of the two cycles, allowing measurement of performance at different combinations of length of time awake and specific circadian phases. We compared this current chronic sleep loss protocol to data from a separate 42.85-hour FD protocol with no intentional sleep loss as a control (Fig. 1) (*8*). In that study, scheduled sleep episodes were 14.28 hours long and scheduled wake episodes were 28.57 hours long (scheduled sleep-to-wake ratio of 1:2 comparable to 8 hours of sleep every 24 hours).

Although the sleep-to-wake ratio in the chronic sleep loss protocol was reduced relative to the control protocol, the 10-hour sleep episodes were longer than each participant's habitual sleep duration. We tested the hypothesis that acute homeostatic regulation of performance over hours was separable from chronic homeostatic regulation over days

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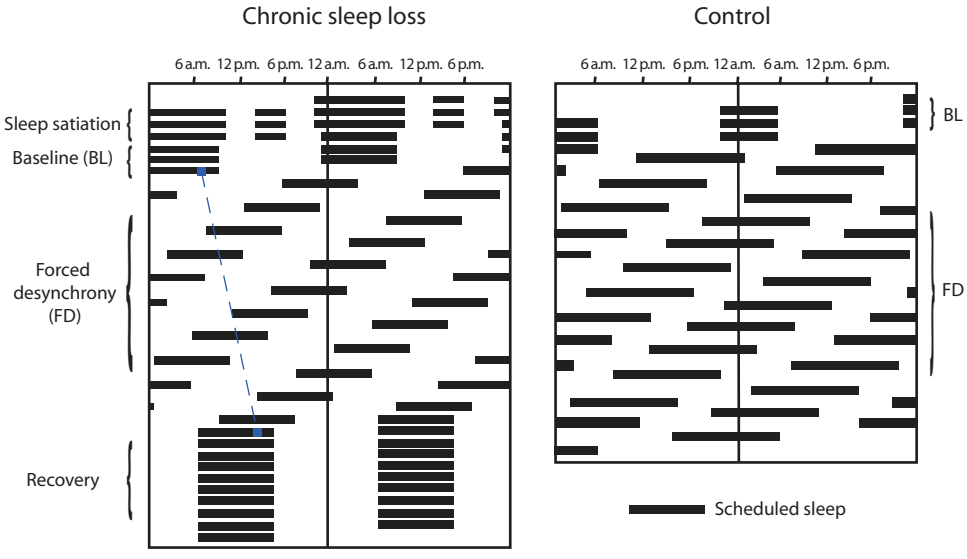

Fig. 1. Double-raster plot demonstrating the timing of sleep in the chronic sleep loss and control protocols. In a raster plot, time in hours is plotted on the horizontal axis and days on the vertical axis; in a double-raster plot, 2 days are included on each horizontal line with the second day also plotted on the left side of the next row. Black horizontal bars indicate scheduled sleep episodes. In the chronic sleep loss protocol, participants were realigned to their habitual phase relation between the sleep-wake and circadian cycles during the recovery (last 10 days); this was adjusted for each participant based on their intrinsic circadian period as determined during the FD portion of the experiment. For example, the blue dotted line represents the drift of a circadian phase marker for a subject with an intrinsic circadian period of ~24.3 hours.

to weeks, in contrast to a single sleep homeostatic mechanism. Within a framework of a single homeostatic mechanism, sleep pressure would rise during wakefulness and incompletely dissipate during sleep within each sleep-wake cycle, secondary to the reduced sleep-to-wake ratio (*10*), and would thus accumulate over weeks on the chronic sleep loss protocol. This framework predicts that performance early in each wake episode would become progressively worse across the 3 weeks. In contrast, in a framework of multiple homeostatic processes, the sleep achieved within each 10-hour sleep opportunity could be enough to completely dissipate the acute homeostatic sleep pressure and restore performance early in the wake episode to baseline levels, but a separate chronic homeostatic process accumulating during the 21-day experiment could be predicted to increase the rate of performance deterioration over consecutive hours awake (*11*).

RESULTS

The psychomotor vigilance task (PVT), a test of sustained attention, was the primary performance measure. Under real-world conditions of chronic sleep restriction, poor PVT performance has been associated with impairments to levels similar to that of driving while intoxicated in other performance measures that may have more obvious ecological validity, such as simulated driving (*12*). The PVT was administered every 4 hours starting 2 hours after waking to nine individuals in the chronic sleep loss group (sleep-to-wake ratio, 1:3.3) and every 2 hours to eight individuals in the control group (sleep-to-wake ratio, 1:2). The primary analyses focused on the median reaction time (RT), a measure that is less sensitive to the effects of acute sleep loss relative to other PVT measures (for example, the mean RT) (*13*) and, therefore, a conservative estimate of the potential impairment induced by chronic sleep loss. To distinguish between the hypotheses of a single versus multiple homeostatic processes, we analyzed the median RT as a function of consecutive hours awake averaged across all circadian phases (Fig. 2A). When comparing the first PVT results at 2 hours awake, performance was near baseline levels across all 3 weeks of chronic sleep loss (two baseline days: median RT = 256 ms; first week: median RT = 256 ms; second week: median RT = 278 ms; third week: median RT = 291 ms) and was not significantly different from the control data with a 1:2 sleep-to-wake ratio (first week: 270 ms; second week: 305 ms; third week: 309 ms; $P = 0.42$). In contrast, when comparing the last performance test of each wake episode, which was administered at 30 consecutive hours awake, there was a marked increase in median RT between the first and the second week on the chronic sleep loss protocol (first week: median RT = 667 ms; second week: median RT = 1954 ms; third week: median RT = 2013 ms). When the chronic sleep loss data were fit with a linear model, there was no significant difference across weeks of the protocol in the y intercept, which reflects the theoretical effect of acute homeostatic sleep pressure at awakening, ignoring the impact of sleep inertia (*10*). This is not consistent with the predictions of a single homeostatic process. However, there was a marked increase in slope after the first week, reflecting slower RTs with increasing hours awake (first week: slope = 24 ms per hour awake; second week: slope = 69 ms per hour awake; third week: slope = 65 ms per hour awake). The differences in slope between the first and the second week were significant ($P < 0.0001$). Other PVT measures showed this pattern as well, including the mean RT, 5th percentile RT, and 95th percentile RT (see Supplementary Material). This analysis indicates that the 10-hour sleep opportunities in the chronic sleep loss protocol were sufficient to dissipate an acute homeostatic process to baseline levels in this task even during the third week, but a separate chronic sleep homeostatic process accelerated the performance deterioration over consecutive hours awake.

In contrast to previous chronic sleep loss protocols, the data also can detail performance within a wake episode as a function of circadian timing. Plasma melatonin was the primary marker of the phase of the circadian pacemaker, with the fitted melatonin maximum assigned a phase of 0°. Figure 3A demonstrates that PVT performance was worst at circadian phases 0° to 60° (corresponding to about 3 a.m. to 7 a.m. during entrained conditions) and it was best at 180° to 240° (corresponding to about 3 p.m. to 7 p.m. during entrained conditions), phases at which the circadian pacemaker strongly promotes sleep and wakefulness, respectively (*14*, *15*). Across both experimental protocols, the amplitude of the circadian oscillation in performance increased with the number of consecutive hours awake such that, after only a few hours awake, the variation in performance across circadian phases was small,

whereas with longer time awake the variation in performance across circadian phases was much larger. This is consistent with previous studies (*5*, *8*). In addition, chronic sleep loss, assessed as both a function of week within the chronic sleep loss protocol and differences between experimental groups (with different sleep-to-wake ratios), increased the amplitude of the circadian performance rhythm. This was evident as a significant four-way interaction of circadian phase, length of time awake, week on the FD protocol, and group on PVT median RT ($P <$

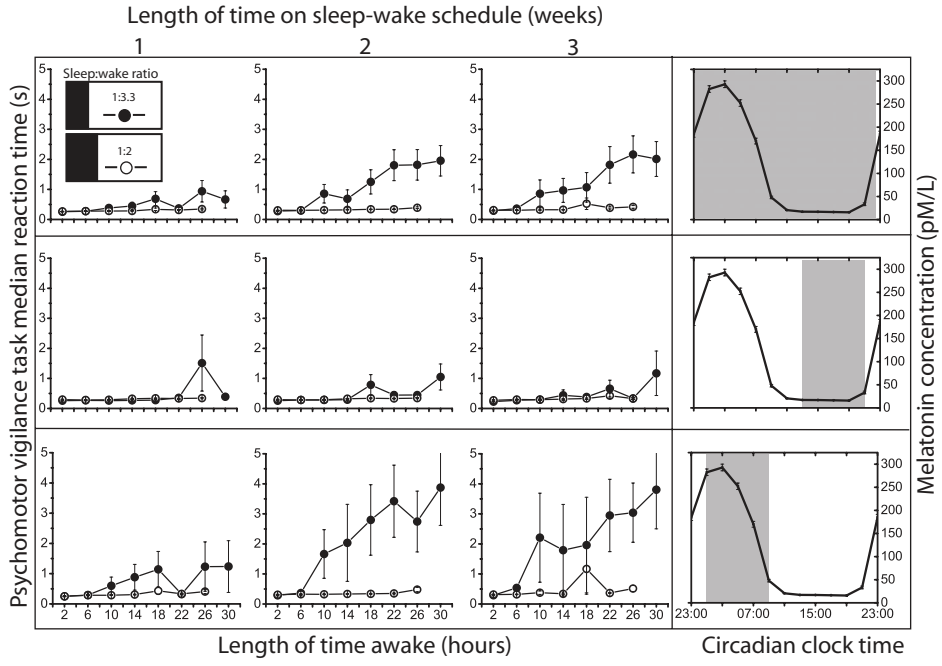

Fig. 2. Separating acute and chronic sleep homeostatic processes: effect of consecutive hours awake on observed PVT median RT (mean and SEM). Weeks on the experimental schedule are shown from left to right. The graphs at the far right show the range of circadian phases for which data are included in each row, using melatonin as a phase marker of the circadian pacemaker. During entrained baseline conditions, the melatonin maximum occurred at about 3 a.m. (**A**) Homeostatic response across all circadian phases. (**B**) Homeostatic response during the circadian afternoon or early evening. (**C**) Homeostatic response during the late circadian night. Independent of circadian phase and across all weeks of the protocol, performance returns to near-baseline levels for at least the first 6 hours after waking. Chronic sleep loss (solid circles) accelerates the decline in performance over consecutive hours awake, predominantly during the late circadian night with remarkably preserved performance during the circadian afternoon or early evening. Variability is greatest with longer consecutive hours awake, weeks of chronic sleep loss, and during the late circadian night. Note that the graphs do not indicate the trajectory of an individual with increasing time awake (accompanied by change in circadian phase) but rather the theoretical homeostatic effect of increasing time awake at a fixed circadian phase. In the control group, there was a slowing of median RT by ~30% between 2 and 26 hours awake, but this deterioration within wake episodes (at an average circadian phase) is not apparent at this scale.

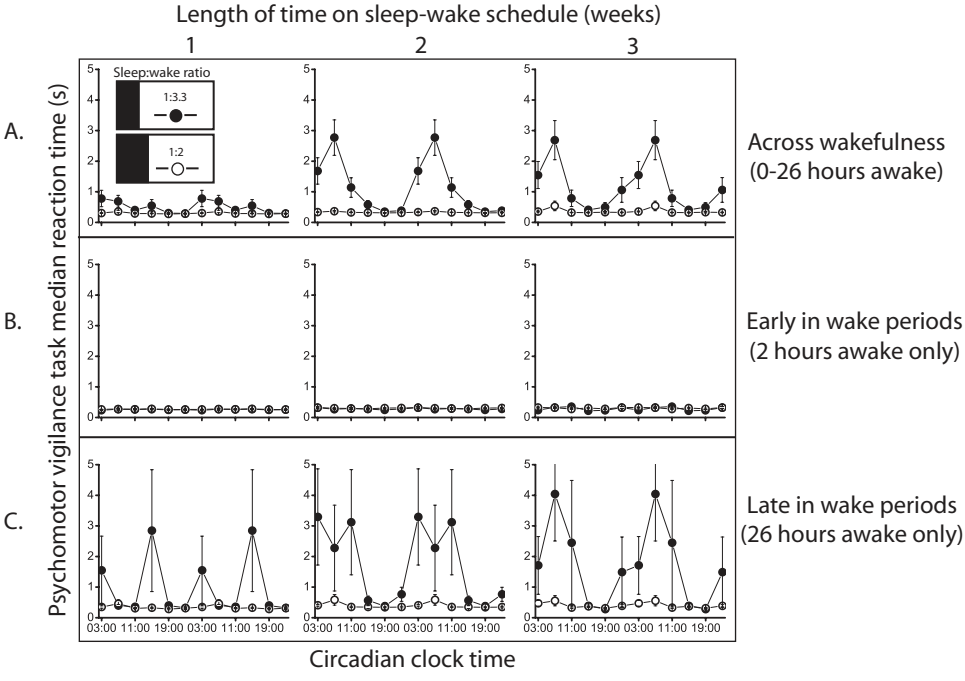

Fig. 3. Circadian rhythm of performance: effect of circadian phase on observed PVT median RT (mean and SEM). Weeks on the experimental schedule are shown from left to right, and two circadian cycles in each panel. (**A**) Circadian oscillation in performance averaged across 26 hours of wakefulness per wake episode. (**B**) Circadian oscillation early in each wake episode at 2 hours awake. (**C**) Circadian oscillation late in each wake episode at 26 hours awake. As can be seen in (B), across all weeks of the protocol, the amplitude of the circadian oscillation is small shortly after waking. However, chronic sleep loss (solid circles) increases the amplitude of the circadian oscillation predominantly after extended wakefulness (C). Chronic sleep loss alone therefore is not sufficient to appreciably increase the circadian amplitude; rather, it intensifies the interaction between acute sleep loss and circadian phase. In the control group, the 116-ms average peak-to-trough difference in the circadian performance rhythm (averaged across 26 hours awake) is not apparent at this scale.

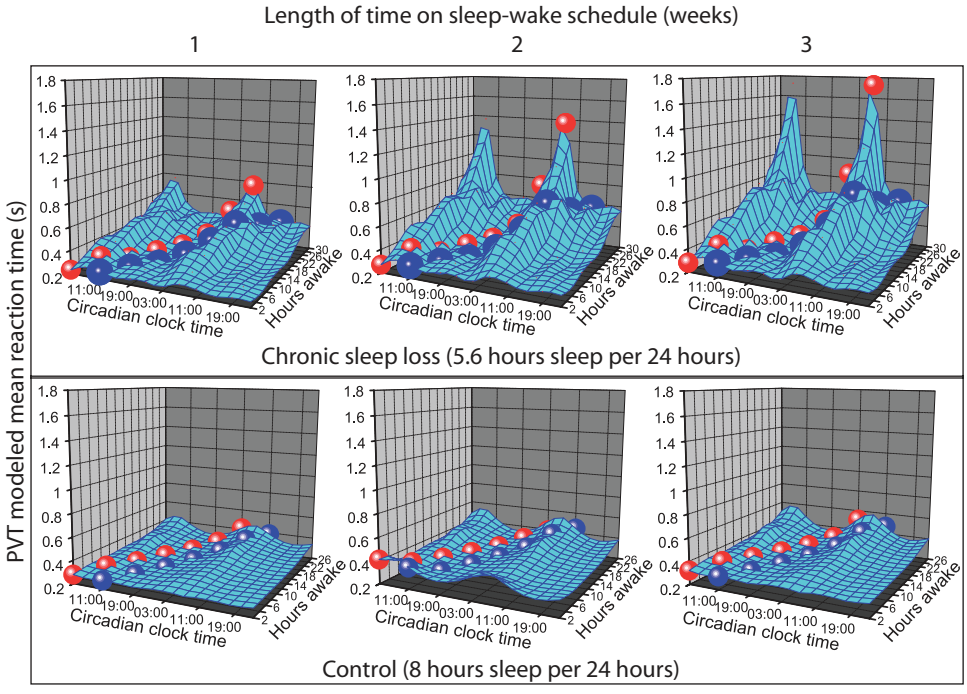

Fig. 4. Circadian and homeostatic regulation of performance. Mixed-effects statistical model predictions of PVT mean RT data at each combination of circadian phase (double plotted) and length of time awake within each week on the FD protocol are shown. Within each week of the chronic sleep loss protocol (top row), circadian amplitude increased with longer consecutive hours awake. Across weeks (left to right within each row), there was a disproportionate deterioration of performance during the late circadian night across 3 weeks of chronic sleep loss. Projected trajectories demonstrate the combination of consecutive hours awake and corresponding circadian time when individuals awaken at their normal entrained circadian time (blue path) and when they awaken 2 hours before the melatonin peak (red path), as may occur during jet lag or night-shift schedules. The cumulative cost of chronic sleep loss is most pronounced during these conditions of circadian misalignment. The 85% average increase in predicted mean RT in the control condition between 2 hours awake during the circadian "day" and 26 hours awake during the circadian "night" is not apparent at this scale.

0.0001). Note that the apparent increase in circadian amplitude with chronic sleep restriction was primarily associated with worsening of the performance nadir in the late circadian night during extended wakefulness (Fig. 3, B and C, and Fig. 4). Other PVT measures also showed this significant four-way interaction, including the mean RT, PVT lapses (trials with RT > 0.5 s), 5th percentile RT, and 95th percentile RT ($P < 0.0001$). The most robust differences were seen between the first and the second week of chronic sleep restriction (Figs. 2 to 4). Acute and chronic sleep loss and adverse circadian phases generally increased the probability of slow RTs within this 10-min PVT, but the fastest possible RTs were relatively preserved (see Supplementary Material). This shift in the rightward tail of the response distribution has been interpreted to reflect an impairment of attention rather than primary visual or motor processes (*16*).

Generalization of our results to predict the average level of impairment that can be expected at a population level requires accounting for interindividual differences. Statistical models can take into account such differences to make predictions about performance. For example, performance at all the different combinations of time awake, circadian phase, and week of sleep restriction can be visualized as potential points in a state space of circadian and homeostatic conditions (Fig. 4). However, as a wake episode unfolds, there is a simultaneous change in the number of hours awake and circadian phase, so individuals can only experience limited combinations of homeostatic pressure and circadian phase within a wake episode. On the basis of the circadian phase at awakening, the expected trajectory of how performance will change throughout the wake episode can be determined. These models are therefore useful for predicting the effects of acute and chronic sleep loss combined with various levels of circadian misalignment, such as occurs during shift-work conditions. Note that the statistical model does not take into account differences in the sex distribution between the chronic sleep restriction group (four female and five male) and the control group (eight male). Although a recent study demonstrated slightly slower RTs in women relative to men, sex differences did not influence the deterioration of performance during acute sleep loss in that study (*17*). Nevertheless, sex differences in response to chronic sleep loss may exist.

In this chronic sleep loss protocol, sleep efficiency [(total sleep time/time in bed) × 100%] was ~90% (mean ± SEM, 90.14 ± 0.08%) for all 3 weeks of the protocol. This sleep efficiency corresponds to about 9 hours of sleep per sleep episode or 5.0 hours of sleep per 24 hours. For the FD in the control group with a 1:2 sleep-to-wake ratio, sleep efficiency was 84.0 ± 0.1%, corresponding to 12 hours of sleep per sleep episode or 6.7 hours of sleep per 24 hours.

DISCUSSION

Our findings demonstrate that the homeostatic regulation of alertness and performance in humans is composed of at least two dissociable components that act on different time scales. Recent animal data support our findings: The short-term homeostatic process acts on the order of hours and may be mediated by accumulating levels of extracellular adenosine in the basal forebrain and other cerebral sites as a product of energy metabolism (*18*–*22*), although this hypothesis has been challenged (*23*). The characteristics of the short-term homeostatic process are similar to the homeostatic regulation of slow-wave sleep (*24*). On longer time scales, the reduced sleep-to-wake ratio of chronic sleep loss (*10*) may cause an up-regulation of adenosine receptor density, sensitizing the system and increasing sleep drive for a given number of consecutive hours awake (*25*, *26*).

Data from this experiment reveal that individuals can develop a chronic sleep debt in the face of apparent full recovery from acute sleep loss. It is common for individuals to have relatively long sleep bouts on weekends or holidays but short sleep episodes on work or school days. Under such conditions, chronically sleep-restricted indi-

viduals may have a false sense of recovery from their previous sleep debt as a result of performing well for the first several hours of a usual waking day. In addition, during circadian phases typically corresponding to afternoon or early evening, the circadian system has the remarkable capacity to override the deleterious effects of previous sleep loss (Fig. 2B). Thus, the short-term restorative properties of recent extended sleep combined with the alerting properties of the normally timed circadian rhythm can mask the effects of chronic sleep loss during a typical waking day. However, during subsequent bouts of extended wakefulness, the cumulative effect of chronic sleep loss may cause performance to deteriorate much more rapidly, particularly during the late circadian night. In addition, these data demonstrate that chronic sleep loss reduces an individual's ability to cope with circadian misalignment from rotating shift schedules or jet lag because the alerting phase of the circadian rhythm may be inappropriately timed to counter the deterioration in performance experienced after several hours awake.

A practical application of this work relates to individuals who work extended hours, such as health care workers, military personnel, emergency response teams, and transportation workers. After such workers remain awake all day, their performance may deteriorate overnight, when increasing consecutive hours of wakefulness combine with the circadian performance nadir to make them increasingly vulnerable to accidents and errors. This degraded performance may be somewhat mitigated if the individual were to have adequate sleep for weeks before this challenge (*27*), as demonstrated by smaller impairments seen in the control group during extended wakefulness. It is important to bear in mind that acute sleep loss alone is hazardous: 19 hours of sustained wakefulness from 8 a.m. to 3 a.m. is associated with performance deficits equivalent to a blood alcohol concentration of 0.05%, and after 24 hours of sustained wakefulness, the performance deficit is equivalent to an alcohol concentration of 0.10% (*28*). Yet, using the metric we have chosen to evaluate the additional impact of chronic sleep loss, these performance deficits from acute sleep loss experienced in the control condition appear indistinguishable from baseline when presented at the same scale as the chronic sleep loss condition. We found that when participants were preloaded with fatigue due to chronic sleep loss, the deterioration in performance during the biological night induced by acute sleep loss dwarfed the impairment induced by acute sleep loss alone in people who were not chronically sleep-restricted. This has important safety implications for the 16% of Americans who routinely sleep 6 hours per night or less (*29*), particularly those in safety-sensitive industries such as long-haul trucking (*30*). Mathematical models that reflect the three-way interaction of chronic sleep loss, long consecutive wake hours, and circadian phase as well as the time course of the decline in performance documented above can aid in the development of work schedules that reduce the probability of occupational errors, injuries, motor vehicle crashes, and other potential adverse health outcomes. In addition, public health education campaigns should emphasize the potentially covert consequences of chronic sleep loss.

MATERIALS AND METHODS

Participants

Nine healthy volunteers were studied (four female and five male) in the chronic sleep loss protocol. Participants were 21 to 34 years old (mean, 27 years) and were medically healthy by history, physical examination, and laboratory testing of hematological or metabolic measures. There was no evidence of psychological disturbance as judged by questionnaires and a clinical interview with a psychologist. They did not have clinical sleep disorders as assessed by questionnaires and one night of screening clinical polysomnography. Inclusion criteria included self-reported habitual sleep duration of 6.5 to 9 hours averaged across the entire week, with no history of night-shift work or transmeridian travel for at least 3 months before enrollment. Participants were maintained on a regular nocturnal sleep schedule (10 hours per night) at times of their choosing at home for at least 3 weeks before entering the research facility, which was verified by wrist actigraphy, sleep logs, and time-stamped voicemail messages left immediately before going to bed and upon waking to minimize self-imposed sleep loss before entering the Intensive Physiological Monitoring (IPM) Unit of the Brigham and Women's Hospital Center for Clinical Investigation research facilities. Only deviations of less than 30 min from this schedule were allowed.

The eight control participants studied in the FD with 1:2 sleep-to-wake ratio were male (ages 18 to 30 years). Their physical exam, laboratory, psychological, and questionnaire screening and eligibility criteria were the same as for the chronic sleep loss protocol. They had 8-hour time in bed at home before entering the IPM. Data from this group have been previously reported (*8*).

For both protocols, participants refrained from alcohol, caffeine, and nicotine for 3 weeks at home and while in the IPM; this was verified by toxicology screening. All participants gave written informed consent. The protocols were approved by the Partners Healthcare Institutional Review Board.

Chronic sleep loss protocol

The chronic sleep loss experiment included a 38-day protocol (Fig. 1) within the IPM. The protocol began with a 12-hour overnight sleep opportunity and a 4-hour daytime nap opportunity for the first 3 days to minimize any residual sleep loss. This was followed by two baseline days with a 10-hour overnight sleep opportunity at the same clock time as their home schedule. The participants then entered the FD segment of the protocol, which lasted 21 calendar days and contained 12 cycles of the 42.85-hour sleep-wake schedule. Participants then had 10 recovery days, consisting of 14 hours of scheduled wakefulness and 10-hour scheduled sleep episodes, which is the same pattern as the two baseline days. Circadian phase estimates using temperature data collected during FD were used to realign the sleep-wake schedule so that recovery sleep episodes occurred at the same circadian phase as during the baseline entrained conditions. During the last baseline day and during the FD segment of the protocol, a technician remained in the room during scheduled wakefulness to minimize inadvertent sleep.

Within each week of the FD protocol, the four scheduled sleep episodes (occurring 42.85 hours apart) and other periodic events in the sleep-wake schedule were relatively evenly distributed across all circadian phases (*9*). The experimental environment is free of time cues to minimize the potential synchronizing influences on the circadian system. Light levels were at ~4 lux during wakefulness and 0 lux during sleep to minimize any circadian phase–shifting effects of light (*31*). Circadian phase was assessed with hourly serum melatonin samples as the primary phase marker and continuous core body temperature measurements via a rectal sensor as a secondary measure. Nonorthogonal spectral analysis (*9*, *32*) of melatonin and temperature data was used to estimate the intrinsic period of each participant's endogenous circadian pacemaker (mean, 24.17 ± 0.21 hours; range, 23.73 to 24.43 hours across all nine participants) and the timing of protocol events relative to the melatonin rhythm.

Psychomotor vigilance task

Participants were tested with 25-min test batteries every 2 hours, starting 2 hours after waking to allow the dissipation of sleep inertia (*33*), which is the cognitive impairment observed immediately on waking. Data from the other performance and mood testing during these batteries are not reported here. Alternating test batteries were used such that the PVT was administered every 4 hours in the chronic sleep loss group and every 2 hours in the control group starting 2 hours after waking. In the PVT, participants are instructed to maintain the fastest possible RTs to a simple visual stimulus. The interstimulus interval involves a high signal rate, randomly varying between 2 and 10 s. Participants sat 57 cm from a monitor screen, measured before each test administration, to ensure a consistent visual angle for all testing. Responses were made with the dominant thumb on a response button, and visual feedback of each RT was provided. Anticipatory responses before the appearance of the target (that is, false alarms) were discouraged, and visual feedback of anticipatory responses was immediately presented on the screen when they occurred. Each administration of the PVT lasted 10 min. The PVT does not display appreciable practice effects (*34*), making it an ideal test to compare performance across protocols that have different frequencies of exposure to the task.

Control group

The protocol for the eight control participants with a 1:2 sleep-to-wake ratio within a 42.85-hour FD protocol (*8*) was conducted in the same facility as the current chronic sleep loss protocol. After three baseline days, consisting of 16 hours of scheduled wakefulness and 8 hours of scheduled sleep, participants underwent 14 cycles of FD with a 42.85-hour sleep-wake cycle but with a "normal" sleep-to-wake ratio of 1:2. Only data from the first 12 cycles of FD were used to match number of FD cycles in the chronic sleep loss protocol. Performance tests were given every 2 hours starting 1.5 hours after scheduled wake time. The data were binned into 4-hour time awake bins so that all data could be included and analyzed identically between the chronic sleep loss protocol and control groups.

Sleep data

Sleep was assessed by polysomnography (Vitaport digital sleep recorder, TEMEC Instruments B.V.). The sampling rate was 256 Hz. The electroencephalogram montage consisted of the electrodes C_3, C_4, O_1, and O_2 referenced to contralateral mastoid A_1 and A_2. Sleep data were visually scored according to standard criteria (*35*). Sleep efficiency was defined as (total sleep time/time in bed) × 100%.

Statistical analysis

The duration of one complete circadian cycle, designated as the estimated intrinsic period of the melatonin rhythm of each participant, was divided into 360°, with the fitted melatonin maximum designated at 0° (about 3 a.m. for an individual with a habitual sleep schedule of 11 p.m. to 7 a.m.). The phase of awakening was calculated for each subject with 90° phase bins to determine the relative alignment between the circadian cycle and the sleep-wake cycle at baseline and throughout the FD protocol. On average, the phase relation between the circadian melatonin rhythm and scheduled events approximated baseline conditions after each calendar week and four sleep-wake cycles of the FD protocol. However, for the purpose of analysis, the exact number of sleep-wake cycles included in each week was determined individually on the basis of circadian phase at awakening for each participant. Performance tests were analyzed with a resolution of 60° circadian phase bins to match the every-4-hour sampling rate of the performance tests across wakefulness.

All administrations of the PVT were identified with length of time awake, week within the FD protocol, and circadian phase in degrees. Mixed-effects statistical modeling was used. Group, length of time awake, circadian phase, and week on the protocol were fixed effects; participant was a random effect to model interindividual differences. This model also takes into account correlation of performance measurements within an individual. We assessed for significant two-way interactions between length of time awake and circadian phase within each week; three-way interactions were determined by the change in the time awake × phase interactions by week, and four-way interactions were determined by differences in the change in the time awake × phase interactions across weeks as a function of group. All analyses were done with SAS PROC MIXED with unstructured correlation structure. From the mixed-effects model, a predicted value for mean RT was determined for each combination of group, time awake, and circadian phase within each week (Fig. 4); the model accounts for the observed interindividual variation in performance. Model-predicted RTs tended to be lower than the observed group means during the late circadian night and long consecutive hours awake, physiological conditions in which variability was highest. Therefore, the model predictions are a conservative estimate of the degree of impairment that can be expected at a population level from sleep loss and circadian misalignment.

SUPPLEMENTARY MATERIAL

www.sciencetranslationalmedicine.org/cgi/content/full/2/14/14ra3/DC1
Fig. S1. Acute and chronic sleep homeostatic effects on PVT reaction time measures.

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He is the incumbent of an endowed professorship provided to Harvard University by Cephalon Inc. and holds a number of process patents in the field of sleep or circadian rhythms (for example, photic resetting of the human circadian pacemaker). Since 1985, he has also served as an expert witness on various legal cases related to sleep and/or circadian rhythms. Patents: beneficiary or inventor on several patents related to assessment and modification of the phase and amplitude of the endogenous circadian rhythm, apparatus for delivering high-intensity light to modify circadian rhythms, a method to modify circadian rhythms with short wavelength light, and a test for evaluating visual function in visually impaired people. 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