The Cumulative Cost of Additional Wakefulness: Dose-Response Effects on Neurobehavioral Functions and Sleep Physiology From Chronic Sleep Restriction and Total Sleep Deprivation

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Objectives: To inform the debate over whether human sleep can be chronically reduced without consequences, we conducted a dose-response chronic sleep restriction experiment in which waking neurobehavioral and sleep physiological functions were monitored and compared to those for total sleep deprivation.

Design: The chronic sleep restriction experiment involved randomization to one of three sleep doses (4 h, 6 h, or 8 h time in bed per night), which were maintained for 14 consecutive days. The total sleep deprivation experiment involved 3 nights without sleep (0 h time in bed). Each study also involved 3 baseline (pre-deprivation) days and 3 recovery days.

Setting: Both experiments were conducted under standardized laboratory conditions with continuous behavioral, physiological and medical monitoring.

Participants: A total of $n = 48$ healthy adults (ages 21–38) participated in the experiments.

Interventions: Nocturnal sleep periods were restricted to 8 h, 6 h or 4 h per day for 14 days, or to 0 h for 3 days. All other sleep was prohibited.

Results: Chronic restriction of sleep periods to 4 h or 6 h per night over 14 consecutive days resulted in significant cumulative, dose-dependent deficits in cognitive performance on all tasks. Subjective sleepiness ratings showed an acute response to sleep restriction but only small further increases on subsequent days, and did not significantly differentiate the 6 h and 4 h conditions. Polysomnographic variables and δ power in the non-REM sleep EEG—a putative marker of sleep homeostasis—displayed an acute response to sleep restriction with negligible further changes across the 14 restricted nights. Comparison of chronic sleep restriction to total sleep deprivation showed that the latter resulted in disproportionately large waking neurobehavioral and sleep δ power responses relative to how much sleep was lost. A statistical model revealed that, regardless of the mode of sleep deprivation, lapses in behavioral alertness were near-linearly related to the cumulative duration of wakefulness in excess of 15.84 h (s.e. 0.73 h).

Conclusions: Since chronic restriction of sleep to 6 h or less per night produced cognitive performance deficits equivalent to up to 2 nights of total sleep deprivation, it appears that even relatively moderate sleep restriction can seriously impair waking neurobehavioral functions in healthy adults. Sleepiness ratings suggest that subjects were largely unaware of these increasing cognitive deficits, which may explain why the impact of chronic sleep restriction on waking cognitive functions is often assumed to be benign. Physiological sleep responses to chronic restriction did not mirror waking neurobehavioral responses, but cumulative wakefulness in excess of a 15.84 h predicted performance lapses across all four experimental conditions. This suggests that sleep debt is perhaps best understood as resulting in additional wakefulness that has a neurobiological "cost" which accumulates over time.

Key Words: chronic sleep restriction, partial sleep deprivation, total sleep deprivation, cognitive performance, subjective sleepiness, cumulative deficits, sleep debt, wake extension, core sleep, sleep need

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INTRODUCTION

THE DEBATE OVER DAILY SLEEP NEED IN MODERN HUMANS IS LONGSTANDING. Although it is well established that sleep cannot be completely eliminated without waking neurobehavioral consequences,[1,2] less is known about the effects of the relatively common practice of chronically reducing time for sleep during the work week[3] or for even longer periods. Questions of whether there are increased waking performance deficits from chronic sleep reduction have substantial relevance to many human endeavors, especially those requiring activities 24 h a day, 7 days a week (e.g., industrial production, transportation, public safety). They have also become of increasing concern for opera-

tions that require high-level cognitive performance at critical times in potentially lethal situations (e.g., health care, military operations, space flight).

The scientific debate over the consequences of chronic sleep restriction has centered on theoretical concepts such as sleep debt,[4,5] sleep tendency,[5] and core sleep versus optional sleep.[6,7] These theoretical concepts have not resolved the issue,[8] however, due to ambiguities in the constructs and a lack of reliable scientific evidence on whether humans can maintain stable behavioral alertness and cognitive functions when daily sleep is reduced across many days. Experimental reports on the effects of long-term chronic sleep restriction have bordered on the anecdotal, lacking adequate sample sizes and control groups. Most have failed to ensure that subjects maintained the assigned sleep/wake schedules; used infrequent, confounded and/or insensitive measures of sleep and waking; and lacked sophisticated time series analyses (for reviews see refs. 9,10). More systematic studies evaluating the cumulative effects of restricting sleep to between 4 h and 6 h per night for up to a week have yielded conflicting results. Those that concluded that there were few if any detrimental effects of chronic sleep restriction on daytime cognitive performance also failed to keep subjects in the laboratory under controlled conditions to ensure that they obtained only the sleep permitted and that they took no stimulants (e.g., caffeine).[11–14] In contrast, those that precisely controlled sleep time and dietary intake by

monitoring subjects throughout the study, found objective evidence of cumulative neurobehavioral effects from sleep restriction to between 4 h and 6 h per night.[10,15,16] No study of chronic sleep restriction between 4 h and 6 h per night has yet been published in which precise experimental control of sleep periods and waking activities was maintained for more than a week. It has remained unclear at what rates neurobehavioral deficits accumulate under chronic sleep restriction, and whether they can reach impairment levels comparable to those found for total sleep deprivation.

Mathematical models of sleepiness and performance based on the two-process model of sleep regulation[17] predict that compensatory homeostatic sleep responses would make it possible to chronically reduce sleep duration without cumulative changes in neurobehavioral functions.[18] This prediction does not appear to be supported by results from laboratory experiments involving a week of sleep limited to 5 h per night.[10,15] Yet, it has been found that losing one night of sleep (i.e., total sleep deprivation) leads to greater neurobehavioral deficits than when the same total amount of sleep is lost across multiple nights of sleep restriction.[16] This suggests that either some adaptation to chronic sleep restriction occurs, or that it is not the amount of cumulative sleep lost that predicts waking neurobehavioral functions.

The possible occurrence of adaptation to sleep restriction needs to be evaluated in chronic paradigms, in which quantitative estimates of the temporal profile of waking responses across days can be reliably obtained. Comparison of the neurobehavioral effects of chronic sleep restriction to those of total sleep deprivation should help to answer the question of whether chronic sleep loss can induce waking neurobehavioral changes and sleep physiological responses equivalent to those found for total sleep loss. We report here the results of dose-response experiments on chronic sleep restriction for 14 consecutive days and total sleep deprivation for 3 days. In these experiments, sleep and wake timing and confounding factors were controlled by having subjects remain in a laboratory (for a cumulative total of 830 days) with continuous behavioral and physiological monitoring, and random assignment to experimental conditions. The experiments had five goals: (1) Determine whether sleep chronically limited to 4 h, 6 h or 8 h per night for 14 consecutive nights results in cumulative changes in waking cognitive performance functions, subjective sleepiness, and sleep physiology; (2) Determine if cumulative changes in cognitive performance, subjective sleepiness, and sleep physiology induced by chronic sleep restriction reach levels obtained after 1, 2 and 3 consecutive nights of total sleep deprivation; (3) Obtain quantitative estimates of inter-individual differences in response to chronic sleep restriction; (4) Identify factors underlying behavioral alertness changes across days for both chronic sleep restriction and total sleep deprivation; and (5) Estimate nightly sleep needed by the subject population to prevent accumulation of waking cognitive deficits resulting from insufficient sleep.

METHODS

Study Design and Participants

Healthy adults ($n = 48$) participated in a chronic sleep restriction experiment or in a total sleep deprivation experiment. They were physiologically and behaviorally monitored in a laboratory in the General Clinical Research Center (GCRC) of the Hospital of the University of Pennsylvania, under controlled conditions and with strict schedules for time in bed (TIB). The sleep restriction experiment involved one adaptation day and two baseline days with 8 h sleep opportunities (TIB 23:30–07:30), followed by randomization to 8 h, 6 h or 4 h periods for nocturnal sleep (TIB ending at 07:30) for 14 days. The total sleep deprivation experiment consisted of one adaptation day and two baseline days with 8 h sleep opportunities (TIB 23:30–07:30), after which subjects were kept awake for 88 h. Both experiments concluded with 3 recovery days.

At all scheduled wake times, subjects were kept awake in the laboratory under continuous behavioral monitoring, and they underwent neu-

robehavioral assessments of cognitive performance, mood and symptom complaints every 2 h. Between test bouts they were allowed to read, watch movies, and interact with laboratory staff to help them stay awake, but no vigorous activities (e.g., exercise) were permitted. In the chronic sleep restriction conditions, normal daylight entered the laboratory but light exposure was relatively low (approximately less than 100 lux). In the 0 h sleep condition, the laboratory was maintained in less than 50 lux of light at all times. During scheduled sleep times, all lights were turned off (less than 1 lux) in every experimental condition. Subjects did not use any caffeine, alcohol, tobacco, and/or medications in the 2 weeks before the experiment, as verified by means of blood and urine screens and questionnaires, and during the experiment, as per the experimental protocol.

Volunteers were screened to ensure they had no medical, psychiatric, or sleep-related disorders and were drug-free. This was determined by history, physical examination and psychological questionnaires, and by clinical blood and urine laboratory tests and toxicological screening. Subjects reported working neither regular night nor rotating shift work within the past 2 years. They also reported not having traveled across time zones in the 3 months before the experiments. The Institutional Review Board of the University of Pennsylvania reviewed and approved the studies, and each subject gave written informed consent.

Subjects randomized to the 8 h sleep periods ($n = 9$; 2 females) were 24.1 ± 2.2 years old (mean $\pm$ s.d.); subjects randomized to the 6 h sleep periods ($n = 13$; 3 females) were 30.1 ± 4.5 years old; and subjects randomized to the 4 h sleep periods ($n = 13$; 1 female) were 27.7 ± 5.4 years old. Subjects in the 0 h sleep condition ($n = 13$; all males) were 27.3 ± 4.6 years old. The subjects in the 8 h sleep period condition were significantly younger than those in the 6 h sleep period condition (one-way ANOVA, $F_{3,44} = 3.16$, $P = 0.034$; Bonferroni post-hoc test, $P = 0.022$). There were no other significant age differences among sleep restriction conditions.

A behavioral estimate of circadian phase position was obtained with a morningness/eveningness questionnaire.[19] Subjects in the 8 h sleep period condition had a morningness/eveningness score of 54.3 ± 8.1 (mean $\pm$ s.d.); those in the 6 h sleep period condition had a score of 52.5 ± 9.6; those in the 4 h sleep period condition had a score of 55.6 ± 13.4; and those in the 0 h sleep condition had a score of 52.8 ± 7.4. There were no significant differences among conditions in morningness/eveningness (one-way ANOVA, $F_{3,44} = 0.28$, $P = 0.84$).

Each subject's average sleep duration when living outside the laboratory in the 5 days prior to the experiment was assessed by means of actigraphy combined with complementary diary reports and time-stamped phone records for time to bed and time awake. Pre-study estimated sleep duration was 7.64 ± 0.65 h (mean $\pm$ s.d.) for subjects in the 8 h sleep period condition; 7.92 ± 0.65 h for subjects in the 6 h sleep period condition; 7.84 ± 0.61 h for subjects in the 4 h sleep period condition; and 7.70 ± 0.87 h for subjects in the 0 h sleep condition. There were no differences among conditions in pre-study sleep duration (one-way ANOVA, $F_{3,44} = 0.38$, $P = 0.77$).

Neurobehavioral Performance

Throughout all experimental conditions, subjects underwent neurobehavioral assessments every 2 h during scheduled wakefulness. Compared to subjects in the 8 h sleep period condition, subjects in the 6 h and 4 h sleep period conditions had one more neurobehavioral test bout per day, scheduled at 00:50, when the subjects in the 8 h sleep period condition were in bed. Subjects in the 0 h sleep condition were tested every 2 h throughout the 88 h of sleep deprivation. Only test bouts in the periods from 07:30 until 23:30 were included in the data analyses.

The neurobehavioral assessment battery included a psychomotor vigilance task[20] to measure behavioral alertness. The psychomotor vigilance task (PVT) is a sustained-attention reaction time task with a random inter-stimulus interval of 2–10 s. Lapses (reaction times greater than 500 ms) were counted per 10 min test bout as a measure of performance

impairment indicative of reduced behavioral alertness.[21] The neurobe-havioral assessment battery also included a computerized digit symbol substitution task[22] to measure working memory. This subject-paced task involves the matching of digits (0–9) to symbols (circle, triangle, etc.). The number of correct responses in 1.5 min was counted to measure working memory performance. A serial addition/subtraction task[23] was included in the assessment battery to measure cognitive throughput. The serial addition/subtraction task is a subject-paced task requiring the completion of 50 mental arithmetic trials. The average number of correct responses per min was used as a neurobehavioral assay of cognitive throughput performance. Further, the neurobehavioral assessment battery included the Stanford Sleepiness Scale.[24] Subjects self-rated their sleepiness on this 7-point scale at the beginning of each test bout. The battery also included the Karolinska Sleepiness Scale.[25] Subjects self-rated their sleepiness on this 9-point scale near the end of each test bout. The results for the Karolinska Sleepiness Scale were very similar to those for the Stanford Sleepiness Scale. Therefore, results pertaining to subjective sleepiness are represented by the Stanford Sleepiness Scale throughout this paper.

For each of the neurobehavioral assays, daily averages over nine test evaluations in the period from 07:30 until 23:30 were computed to assess the profiles of sleepiness and performance across days of sleep restriction. All subjects in each condition had complete data for the psychomotor vigilance task, the Stanford Sleepiness Scale, and the digit symbol substitution task. For the serial addition/subtraction task, complete data were available for 8 of the 13 subjects in the 0 h sleep condition and for all subjects in the chronic sleep restriction conditions. There were no significant differences at baseline among the four conditions (one-way ANOVA) for the psychomotor vigilance task ($F_{3,44} = 2.00$, $P = 0.13$), the Stanford Sleepiness Scale ($F_{3,44} = 0.44$, $P = 0.73$), and the serial addition/subtraction task ($F_{3,36} = 2.12$, $P = 0.12$). Subjects in the 6 h sleep period condition performed the digit symbol substitution task slightly less well at baseline than those randomized to the 8 h and 4 h sleep period conditions ($F_{3,44} = 2.83$, $P = 0.049$; Bonferroni post-hoc tests, $P = 0.19$ and $P = 0.14$, respectively).

Sleep Architecture

Polysomnography. Polysomnographic (PSG) recordings were made during the third baseline sleep period and during 10 of the 14 restricted sleep periods (days 1, 2, 4, 5, 7, 8, 10, 11, 13 and 14). Only subjects with no more than 4 condition nights of missing data were included in PSG analyses. Thus, we used the PSG data of 7 subjects in the 8 h sleep period condition, 8 subjects in the 6 h sleep period condition, and 9 subjects in the 4 h sleep period condition. For these subjects, data for 1 night of PSG recording were missing on average. Sleep records were scored using conventional criteria,[26] with sleep onset conservatively defined by the occurrence of at least three consecutive 30 s epochs of stage 2-4 or REM sleep. There were no significant differences (one-way ANOVA) among conditions in key variables describing baseline sleep: total sleep time ($F_{2,21} = 1.78$, $P = 0.19$), stage 1 sleep ($F_{2,21} = 0.65$, $P = 0.53$), stage 2 sleep ($F_{2,21} = 1.05$, $P = 0.37$), slow-wave sleep ($F_{2,21} = 0.39$, $P = 0.68$), REM sleep ($F_{2,21} = 1.74$, $P = 0.20$), sleep latency ($F_{2,21} = 1.95$, $P = 0.17$), slow-wave sleep (SWS) latency ($F_{2,21} = 1.19$, $P = 0.33$), REM sleep latency ($F_{2,21} = 0.58$, $P = 0.57$), and wakefulness after sleep onset ($F_{2,21} = 1.33$, $P = 0.29$).

Non-REM EEG delta power. The C3 derivation of the EEG was sampled at 128 Hz and subjected to spectral analysis in 2 s bins after removal of artifacts. Power spectra were averaged across 30 s epochs. For each night, power in the δ band (0.5–4.0 Hz) was totaled over all epochs of non-REM (stages 2–4) sleep, as a marker of sleep homeostasis.[17] For one subject in the 6 h sleep period condition, EEG signal quality was insufficient for reliable power spectral analysis. Thus, δ power data were available for a total of 23 subjects in the 8 h, 6 h and 4 h sleep period conditions.

Data Analyses

Traditional repeated-measures analysis of variance (ANOVA) is not concerned with the temporal arrangement (i.e., order and intervals) of data points, making this technique poorly suited for distinguishing consistent, cumulative changes from error variance in the data. Moreover, repeated-measures ANOVA assumes that the response to the experimental conditions is homogeneous among subjects. Thus, inter-individual differences in the effects of sleep deprivation[8] are ignored. Traditional statistical regression techniques overcome the temporal arrangement problem, but do not readily handle inter-individual differences. In order to be able to also quantify inter-individual variability in the responses to chronic partial and total sleep loss, we applied mixed-effects regression models[27,28] for time series analysis. By incorporating random effects, these models allow proper separation of between-subjects (i.e., inter-individual) and within-subjects (i.e., temporal) variance in the data. As an additional advantage, mixed-effects regression models do not require missing data to be filled in. Furthermore, these models provide a framework for empirical Bayes estimation[29] of subject-specific parameters for temporal profiles across days of sleep restriction.

Neurobehavioral variables. The following non-linear mixed-effects model was fitted to the neurobehavioral performance data y, expressed as difference from baseline, for each neurobehavioral assay:

$$(1) \quad y_t \sim \beta \cdot t^{\theta}$$

where t denotes days of sleep restriction. The parameter β is a normally distributed random effect with condition-specific mean representing rate of change, used to quantify the build-up of neurobehavioral performance impairment across days of sleep restriction for each chronic sleep restriction condition. The parameter θ represents curvature in the response profile, which is necessary to accommodate any non-linearity in the metric of the outcome variable y. A single model was fitted for the three sleep restriction conditions, and a separate model was fitted for the total sleep deprivation condition. For statistical testing of differences among the 8 h, 6 h and 4 h sleep restriction conditions in the rate of change across days, the condition-specific estimates for β were compared using an F test followed by pair-wise contrasts.

Sleep variables. To analyze changes in sleep variables over the 10 restricted sleep periods during which polysomnographic recordings were made, the following linear mixed-effects model was fitted to the data y for each sleep variable:

$$(2) \quad y_t \sim \beta \cdot t + \alpha$$

where t denotes days of sleep restriction. Parameter α is a normally distributed random effect with condition-specific mean representing the acute change in the outcome variable y from baseline to the first restricted sleep period, as resulting from the acute manipulation of time in bed. Parameter β is a normally distributed random effect with condition-specific mean representing the rate of change across subsequent days; this parameter quantifies progressive changes in sleep physiology across days of sleep restriction. A single model was fitted for the 8 h, 6 h and 4 h sleep period conditions. For statistical testing of differences among these conditions in the acute response to sleep restriction, the condition-specific estimates for α were compared using an F test. For statistical testing of differences in the rate of change across days, the condition-specific estimates for β were compared using an F test.

RESULTS

Cognitive Performance

Chronic sleep restriction conditions. Chronic restriction of the nocturnal sleep period to either 6 h or 4 h per day for 14 days resulted in significant cumulative performance deficits relative to the 8 h sleep period condition (Figure 1). Significant differences among conditions in the

rate of change across days (parameter β in equation (1)) were found for psychomotor vigilance task performance ($F_{2,30} = 3.67$, $P = 0.037$), digit symbol substitution task performance ($F_{2,30} = 5.33$, $P = 0.010$), and serial addition/subtraction task performance ($F_{2,30} = 6.19$, $P = 0.006$).

Subjects allowed an 8 h sleep period per night displayed only minor, non-significant increases in lapses of behavioral alertness over the 14 days. The statistically estimated mean of β in equation (1) for the 8 h sleep period condition was not significantly different from zero ($t_{30} = 0.77$, $P = 0.45$) for the psychomotor vigilance task (Figure 1A). Subjects in the 8 h sleep period condition demonstrated normal performance learning curves on the digit symbol substitution task (Figure 1C) and the serial addition/subtraction task (Figure 1D). In contrast, subjects in the 4 h sleep period condition displayed escalating numbers of lapses in behavioral alertness and decreasing cognitive accuracy and speed across the 14 days. The magnitude of changes in performance over days of sleep restriction in the 6 h sleep period condition was between that observed in the 8 h and 4 h sleep period conditions.

For PVT lapses, the subject-specific values of the rate of change β in equation (1) were statistically determined with empirical Bayes estimation.[29] To examine the relationship between pre-study sleep duration and the subject-specific rate of change in behavioral alertness over the 14 days of sleep restriction, these subject-specific β values were correlated with habitual sleep time (estimated by actigraphy combined with diary reports and phone records during the 5 days prior to the experiment). Partial correlation, controlling for experimental condition, revealed a modest but significant positive relationship between average sleep dura-

tion in the 5 days prior to the experiment and rate of increase in PVT lapses over the 14 days of sleep restriction ($r_{32} = 0.29$, $P = 0.048$). This suggests that those subjects who habitually slept longest tended to be more affected by the 14 days of imposed sleep restriction.

Chronic sleep restriction versus total sleep deprivation. In the 4 h sleep period condition, lapses in behavioral alertness and reductions in working memory performance reached levels equivalent to those observed after 2 nights without sleep (Figures 1A, 1C). Cognitive throughput performance after 14 days of sleep restriction was equivalent to that observed after 1 night without any sleep (Figure 1D). Subjects in the 6 h sleep period condition also reached levels of impairment equivalent to those observed after 1 night of total sleep loss for lapses in behavioral alertness and working memory performance (Figures 1A, 1C).

For the 8 h, 6 h and 4 h sleep period conditions, curvature (parameter θ in equation (1)) was statistically estimated to be 0.78 ± 0.04 for psychomotor vigilance task performance, 0.59 ± 0.04 for digit symbol substitution task performance, and 0.45 ± 0.04 for serial addition/subtraction task performance (estimate ± s.e.). For the 0 h sleep condition, curvature was statistically estimated to be 0.57 ± 0.19 for psychomotor vigilance task performance, 0.74 ± 0.12 for digit symbol substitution task performance, and 0.67 ± 0.12 for serial addition/subtraction task performance (estimate ± s.e.). These values indicate that cognitive performance impairment accumulated near-linearly over days for all four experimental conditions, with slight differences between chronic sleep restriction and total sleep deprivation and among cognitive performance tasks.
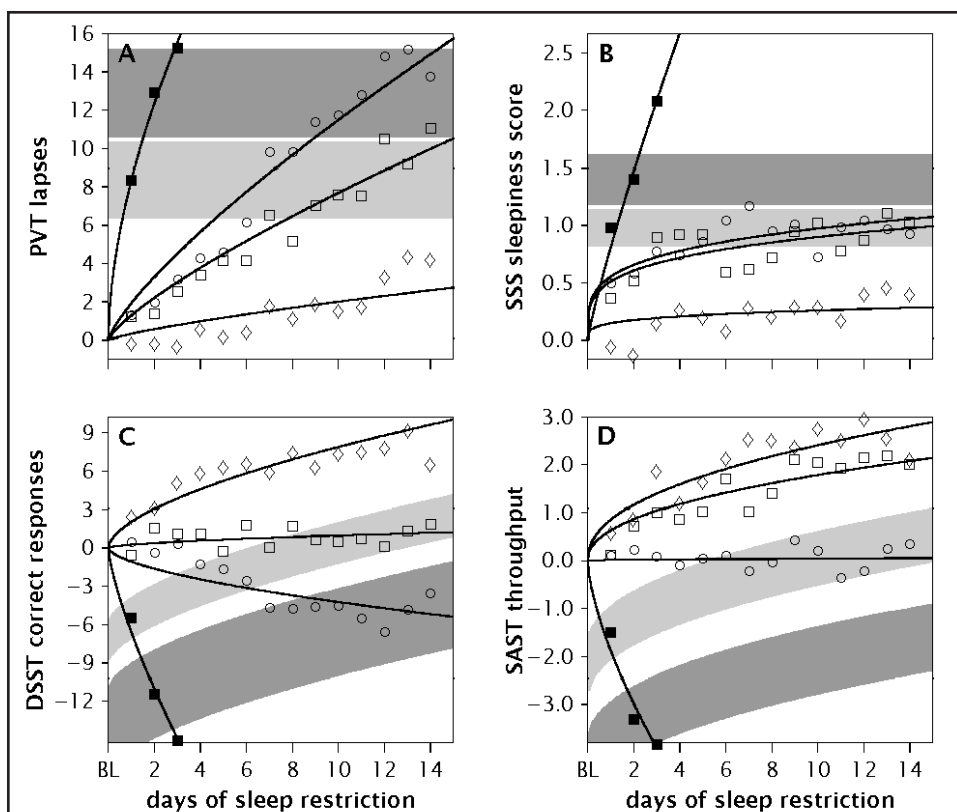

Figure 1—Neurobehavioral responses to varying doses of daily sleep. Four different neurobehavioral assays served to measure cognitive performance capability and subjective sleepiness. Each panel displays group averages for subjects in the 8 h (◊), 6 h (□), and 4 h (○) chronic sleep period conditions across 14 days, and in the 0 h (■) sleep condition across 3 days. Subjects were tested every 2 h each day; data points represent the daily average (07:30–23:30) expressed relative to baseline (BL). Panel A shows psychomotor vigilance task (PVT) performance lapses; panel B shows Stanford Sleepiness Scale (SSS) self-ratings; panel C shows digit symbol substitution task (DSST) correct responses; and panel D shows serial addition/subtraction task (SAST) correct responses per min. Upward corresponds to worse performance on the PVT and greater sleepiness on the SSS, and to better performance on the DSST and the SAST. The curves through the data points represent statistical non-linear model-based best-fitting profiles of the response to sleep deprivation (equation (1)) for subjects in each of the four experimental conditions. The mean ± s.e. ranges of neurobehavioral functions for 1 and 2 days of 0 h sleep (total sleep deprivation) are shown as light and dark gray bands, respectively, allowing comparison of the 3-day total sleep deprivation condition and the 14-day chronic sleep restriction conditions. For the DSST and SAST, these gray bands are curved parallel to the practice effect displayed by the subjects in the 8 h sleep period condition, to compensate for different amounts of practice on these tasks.

Subjective Sleepiness

Chronic restriction of the nocturnal sleep period to either 6 h or 4 h per day for 14 days resulted in a relatively small but significant build-up of subjective sleepiness, as measured with the Stanford Sleepiness Scale (SSS) relative to the 8 h sleep period condition (Figure 1B). Among the three sleep restriction conditions, a significant difference was found in the rate of change across days ($F_{2,30} = 4.26$, $P = 0.024$). Subjects in the 8 h sleep period condition displayed only minor, non-significant increases in self-rated sleepiness: The statistically estimated condition-specific mean of β in equation (1) was not significantly different from zero ($t_{30} = 1.32$, $P = 0.20$). Similarity in the rate of change across days was observed for the 6 h and 4 h sleep period conditions ($F_{1,30} = 0.10$, $P = 0.75$).

The average response to 3 days of total sleep deprivation spanned more than 2 units on the Stanford Sleepiness Scale, while the response to 14 days of sleep restricted to 6 h or 4 h per day was only approximately 1 unit on this scale. In contrast to cognitive performance measures, the curvature (parameter θ in equation (1)) of the response to sleep loss over days was considerably different for chronic sleep restriction versus total sleep deprivation. The curvature for subjective sleepiness as assessed by the SSS was statistically estimated to be 0.86 ± 0.14 for the 0 h sleep condition, and 0.24 ± 0.04 for the 8 h, 6 h and 4 h sleep period conditions (θ estimate ± s.e.). Thus, the profile of subjective sleepiness across days was near-linear for the 0 h sleep condition, while it was near-saturating for the 4 h and 6 h sleep period conditions (Figure 1B).

Results for the Karolinska Sleepiness Scale (KSS) were nearly identical to those found for the SSS. Among the three sleep restriction conditions, a significant difference was found for the KSS in the rate of change across days ($F_{2,30} = 7.76$, $P = 0.002$). Subjects in the 8 h sleep period condition displayed only minor, non-significant increases in self-rated sleepiness ($t_{30} = 0.56$, $P = 0.58$). Again, similarity in the rate of change across days was observed for the 6 h and 4 h sleep period conditions ($F_{1,30} = 1.55$, $P = 0.22$). The curvature for KSS responses to sleep loss was statistically estimated to be 0.81 ± 0.16 for the 0 h sleep condition, and 0.16 ± 0.03 for the 8 h, 6 h and 4 h sleep period conditions (θ estimate ± s.e.). Thus, as with the SSS, the profile of subjective sleepiness rated on the KSS was near-linear across days for the 0 h sleep condition, while it was near-saturating for the 4 h and 6 h chronic sleep restriction conditions.

Sleep Physiology

The temporal dynamics of polysomnographically recorded sleep periods across days of sleep restriction are shown in Figure 2. Polysomnographic assessments of total sleep time, based on a conservative criterion to determine sleep onset (at least three consecutive 30 s epochs of stage 2–4 or REM sleep), showed that we were successful in differentially reducing sleep in the three chronic sleep restriction conditions (Figure 2A). There were condition-specific acute responses (parameter α in equation (2)) in almost all sleep variables as a result of the acute change of time in bed from baseline to the first restricted sleep period. Significant differences among conditions in response to the first night of sleep restriction were found for total sleep time ($F_{2,16} = 135.6$, $P < 0.001$), stage 1 sleep ($F_{2,16} = 12.3$, $P < 0.001$), stage 2 sleep ($F_{2,16} = 29.2$, $P < 0.001$), REM sleep ($F_{2,16} = 12.9$, $P < 0.001$), and total δ power in the non-REM sleep EEG ($F_{2,15} = 5.29$, $P = 0.018$), but not for SWS ($F_{2,16} = 0.18$, $P = 0.84$).

Across the 14 days of sleep restriction, only marginal additional changes were observed in sleep architecture (parameter β in equation (2)). In the 8 h sleep period condition, stage 1 sleep decreased ($t_{16} = -2.49$, $P = 0.024$) while stage 2 sleep ($t_{16} = 2.18$, $P = 0.045$) and REM sleep ($t_{16} = 2.41$, $P = 0.029$) increased, although the magnitudes of these changes were small (Figures 2B, 2C, 2E). REM latency decreased by an average of 2.2 min per day in the 4 h sleep period condition ($t_{16} = -7.55$, $P < 0.001$), but did not change significantly over days in the 6 h and 8 h sleep period conditions. Slow-wave sleep (SWS) increased slightly but progressively over days ($t_{16} = 3.98$, $P = 0.001$) in the 6 h sleep period condition; no significant systematic changes in SWS were found across days of sleep restriction in the 8 h and 4 h sleep period conditions (Figure 2D).

For total δ power in the non-REM sleep EEG (Figure 2F), no significant progressive changes across days of sleep restriction were observed in any of the three chronic sleep restriction conditions ($|t_{15}| \leq 1.61$, $P > 0.13$). The level of δ power observed in the non-REM sleep EEG during recovery sleep after the 0 h sleep condition was considerably higher than that observed during sleep across days in the 6 h and 4 h sleep

period conditions. Total δ power during the first 4 h of nocturnal recovery sleep after 88 h of total sleep deprivation was 172% ± 11% of baseline (mean ± s.e.). This was significantly more than the average for total δ power during sleep chronically restricted to 4 h per night ($F_{1,18} = 5.40$, $P = 0.032$). Thus, the δ power response to total sleep deprivation was greater than the δ power response to chronic sleep restriction (Figure 2F). This observation demonstrates that the absence of δ power accumulation over days in the 6 h and 4 h sleep restriction conditions was not merely an artifact related to limited brain capacity for generating δ power.

Cumulative Sleep and Cumulative Sleep Loss

To understand the nature of the relationship between daily sleep dose and the build-up of neurobehavioral performance impairment, we considered the cumulative build-up of sleep and wake time over days in the four different experimental conditions (Figure 3). First, the accumulation of polysomnographically-recorded total sleep time across days of sleep restriction was assessed for each condition. As expected, cumulative total sleep time increased near-linearly over days in the 8 h, 6 h and
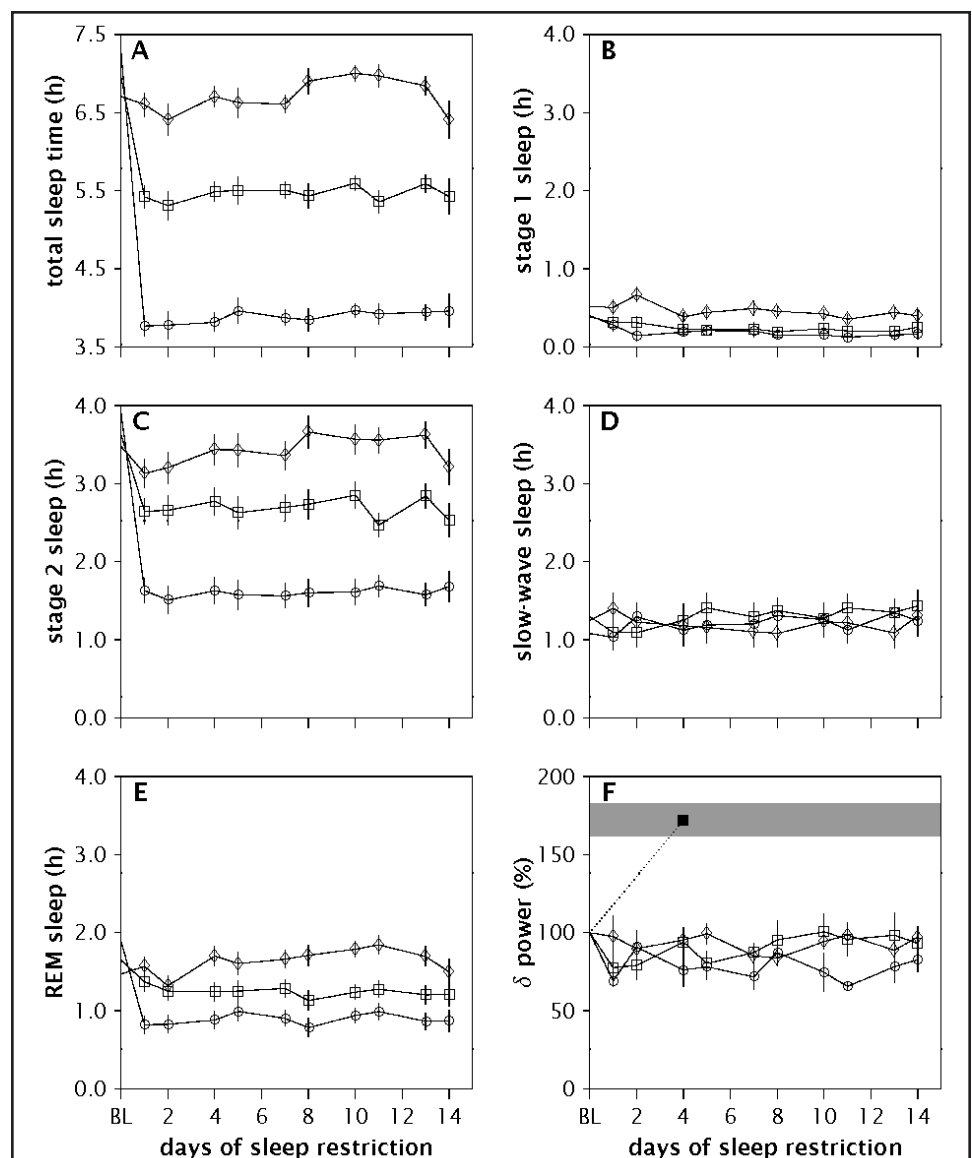

Figure 2—Sleep architecture responses to varying doses of daily sleep. The panels display sleep variables assessed from polysomnographic recordings during baseline (BL) sleep and across 10 of the 14 restricted sleep periods. Panel A shows total sleep time (in h); panels B–E show different stages of sleep (in h); and panel F displays total δ power in the non-REM sleep EEG (as % of baseline). Daily means ± s.e. are shown for subjects in the 8 h (◇), 6 h (□), and 4 h (○) sleep period conditions. Panel F also shows the mean (■) and the mean ± s.e. range (gray band) for total δ power in the first 4 h of recovery sleep after 88 h of total sleep deprivation, which was 172% ± 11% of baseline (mean ± s.e.). This was significantly more than the average for total δ power during sleep chronically restricted to 4 h per day ($F_{1,18} = 5.40$, $P = 0.032$).

4 h sleep period conditions (Figure 3A). This is a direct result of the nearly flat temporal profiles for polysomnographically assessed total sleep time observed in these conditions (Figure 2A).

The accumulation of sleep loss across days of sleep restriction was also calculated. For each subject, we compared total sleep time to habitual sleep time (estimated by actigraphy combined with diary reports and phone records during the 5 days prior to the experiment), and defined the difference as sleep loss. Figure 3B shows the accumulation of sleep loss across days of sleep restriction. It is noteworthy that cumulative sleep loss over 14 days in the 4 h sleep period condition was significantly greater than cumulative sleep loss over 3 days in the total sleep deprivation condition ($t_{20} = 10.58$, $P < 0.001$).

In order to compare cumulative sleep loss (Figure 3B) to cumulative neurobehavioral functions during chronic sleep restriction, we focused

Figure 3—Cumulative build-up of total sleep time, sleep loss and wake time extension across days of sleep restriction and total sleep loss. Panel A shows cumulative total sleep time (in h) derived from polysomnographic recordings (i.e., a cumulative representation of Figure 2A). Panel B shows cumulative sleep loss relative to habitual sleep duration, that is, all hours of sleep habitually obtained (as measured at home during the 5 days prior to the experiment), but not received due to sleep restriction in the experiment. Panel C shows cumulative wake extension relative to habitual wake duration, that is, all consecutive hours of wakefulness in excess of the habitual duration of a wakefulness period. Daily means are shown for subjects in the 8 h (◇), 6 h (□), 4 h (○) and 0 h (■) sleep period conditions. Panel B also shows the mean ± s.d. range (gray band) of cumulative sleep loss (relative to habitual sleep duration) after 3 days in the 0 h sleep condition, which was 23.1 ± 2.6 h (mean ± s.d.). This was significantly less than the cumulative sleep loss after 14 days in the 4 h sleep period condition ($t_{20} = 10.58$, $P < 0.001$).

on performance on the PVT (Figure 1A), because this measure of behavioral alertness displayed no learning curve and no significant cumulative impairment in the 8 h sleep period condition. PVT performance lapses showed evidence of decreased behavioral alertness as a sleep dose-dependent, near-linear function of the number of days of sleep restriction (Figure 1A). This could indicate that the development of neurobehavioral performance deficits over days of sleep restriction may be accounted for solely by cumulative sleep loss. It would then be predicted, however, that the greatest performance impairment should be observed during days 7–14 in the 4 h sleep period condition, when cumulative sleep loss was greater in this condition than in the 0 h sleep condition (Figure 3B). Even after 14 days, however, performance deficits in the 4 h sleep period condition did not exceed those observed after 3 days in the total sleep deprivation condition (Figure 1A). Thus, cumulative sleep loss cannot by itself explain the profiles of waking neurobehavioral performance impairment for both chronic sleep restriction and total sleep deprivation.

Among experimental conditions, there was a high degree of covariation between reductions of total sleep time and reductions of stage 1, stage 2 and REM sleep (cf. Figures 1A, 1B, 1C, 1E), and a relative lack of variation in SWS and non-REM δ power (Figures 1D, 1F). By the same reasoning as for cumulative sleep loss, therefore, the cumulative loss of any of these components of sleep cannot explain the observed profiles of waking neurobehavioral performance impairment in all four experimental conditions.

Cumulative Additional Wakefulness

Since the cumulative loss of sleep time did not parsimoniously explain the rate of change in PVT performance for the chronic sleep restriction conditions as well as the total sleep deprivation condition, we focused on calculation of cumulative wake time extension (Figure 3C). For every subject, the duration of each continuous period of wakefulness during the experiment was compared to habitual wake time (which was defined as 24 h minus habitual sleep time). Wake extension was defined as the difference between the duration of each continuous wake period and the duration of habitual wake time. Accordingly, cumulative wake time extension was calculated as the sum of all consecutive hours of wakefulness extending beyond the habitual duration of wakefulness each subject was accustomed to at home. In the 8 h, 6 h and 4 h sleep restriction conditions, this yielded the same results as for cumulative sleep loss, because the definitions of cumulative wake extension and cumulative sleep loss were arithmetically equivalent. For the 0 h sleep condition (i.e., total sleep deprivation), however, each day without sleep added 24 h to the cumulative wake extension. Thus, over 3 days with 0 h sleep, cumulative wake extension was equal to 72 h for each subject, while cumulative sleep loss was only 23.1 ± 2.6 h (mean ± s.d.). This illustrates that cumulative sleep loss and cumulative wake extension are different constructs that can have different quantitative values, depending on the manner in which sleep loss occurs (cf. Figures 3B and 3C).

As described above, the two modes of sleep loss yielded similar maximum deficits for PVT performance (Figure 1A), but chronic sleep restriction resulted in much greater cumulative sleep loss than did 3 days of total sleep deprivation (Figure 3B). By focusing on cumulative wake extension rather than cumulative sleep loss, we sought to determine if it was the direct cost of additional wakefulness that could reconcile the PVT performance profiles for these different modes of sleep loss. Indeed, the changes in behavioral alertness over days of sleep restriction (Figure 1A) had a greater similarity with the temporal profiles of cumulative wakefulness extension (Figure 3C) than with the temporal profiles of cumulative sleep loss (Figure 3B). For quantitative investigation of this discovery, a statistical model was developed to describe lapses in behavioral alertness (Figure 1A) as a function of cumulative additional wakefulness across all four experimental conditions.

We postulated that the build-up of neurobehavioral deficits was not caused by sleep loss directly, but rather by wakefulness in excess of a (subject-specific) critical wake period, that is, a maximum period during
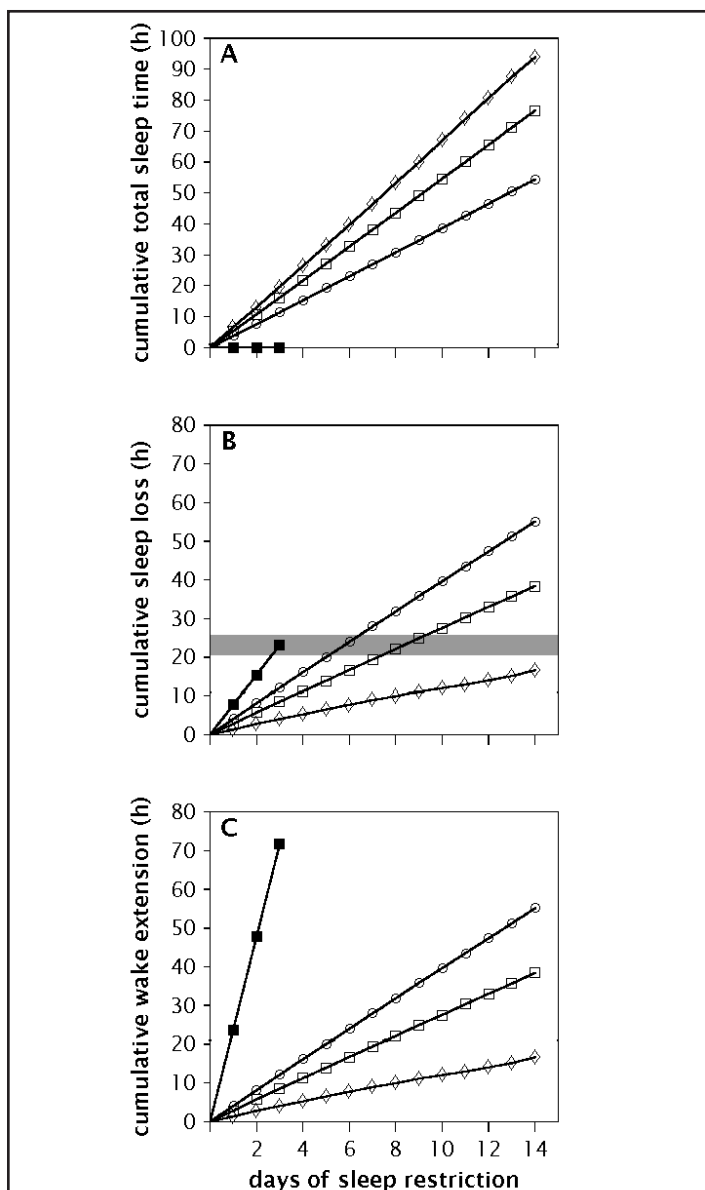
which stable neurobehavioral functioning could be maintained in our healthy young adult subjects. Cumulative excess wakefulness was defined as the sum of all hours of wakefulness in excess of this critical wake period. This construct was similar to cumulative wake extension, but did not rely on assessment of habitual wake duration for establishing the critical wake period beyond which neurobehavioral impairment would accumulate. Instead, the postulated critical wake duration was estimated from the available data.

In the statistical model we developed, parameter ξ was defined as the (*a priori* unknown) critical wake duration (i.e., the postulated maximum period of stable waking neurobehavioral functioning). Cumulative excess wakefulness Σ in the 8 h, 6 h and 4 h sleep period conditions was then obtained by:

$$(3a) \quad \Sigma_t = (24\,h - \xi)\,t - CTST_t$$

where t denotes days of sleep restriction. The variable $CTST_t$ represents cumulative total sleep time (measured polysomnographically) as a function of t. Over days of sleep restriction, cumulative excess wakefulness was equivalent to cumulative sleep loss relative to a critical daily sleep duration of $24\,h - \xi$. In the 0 h sleep condition, however, each day without sleep (beyond the critical wake duration ξ) added 24 h to the cumulative excess wakefulness. Thus, in the 0 h sleep condition, cumulative excess wakefulness Σ was given by:

$$(3b) \quad \Sigma_t = 24\,h \cdot t$$

where again t denotes days of sleep restriction.

A non-linear mixed-effects model[27,28] was formulated to describe lapses in behavioral alertness as a function of cumulative excess wakefulness:

$$(4) \quad y_t \sim \gamma\,(\Sigma_t)^\theta$$

where y denoted PVT performance lapses (expressed as difference from baseline), and θ was a parameter quantifying curvature (as in equation (1)). The parameter γ was a normally distributed random effect representing the rate of increase in PVT lapses per hour of cumulative excess wakefulness. The critical wake duration ξ (i.e., the postulated maximum period of stable waking neurobehavioral functioning) was incorporated in equation (4), via equation (3a), as a second normally distributed random effect. These random effects allowed inter-individual differences in the rate of increase in PVT lapses and in the critical wake duration.[8,30]

The statistically estimated value for ξ was 15.84 ± 0.73 h (estimate $\pm$ s.e.). For the subject population in our experiments, limiting daily wakefulness to this critical wake duration would be expected to prevent the build-up of neurobehavioral deficits. Accordingly, daily sleep need to prevent cumulative neurobehavioral deficits in these subjects would appear to be $24\,h - \xi = 8.16 \pm 0.73$ h (estimate $\pm$ s.e.). The statistically estimated standard deviation over subjects for ξ was 3.58 ± 1.19 h (estimate $\pm$ s.e.); this

standard deviation reflects considerable inter-individual variability in the postulated critical wake duration ξ. The subject-specific values for ξ, statistically determined with empirical Bayes estimation,[29] were similar to the subject-specific habitual wake durations (derived from average sleep durations in the 5 days prior to the experiment). The difference between habitual wake duration and critical wake duration ξ was 0.1 ± 0.5 h (mean $\pm$ s.e.), which was not significantly different from zero ($t_{23} = 0.17$, $P = 0.86$).

Taking into account between-subjects variance in ξ and γ, the statistical model in equation (4) explained 83.0% of the variance in the PVT data (Figure 1A). The value for curvature θ was 0.67 ± 0.05 (estimate $\pm$ s.e.). Thus, across days of sleep restriction, the build-up of psychomotor vigilance performance impairment in all four experimental conditions was well approximated by a single near-linear function of cumulative excess wakefulness. This is illustrated in Figure 4, which shows PVT performance lapses for all subjects as a function of cumulative sleep debt (Figure 4A), and as a function of cumulative excess wakefulness (Figure 4B). When expressed as a function of cumulative sleep debt—the sum of all hours of sleep loss relative to the above-estimated subject-specific daily sleep need—the neurobehavioral response to chronic sleep restriction appeared to be fundamentally different than the neurobehavioral response to total sleep deprivation (Figure 4A). When expressed as a function of cumulative excess wakefulness, however, the neurobehavioral responses to chronic sleep restriction and to total sleep deprivation were well approximated by a single near-linear model (Figure 4B). This illustrates the monotonic, near-proportional relationship between cumulative excess wakefulness and neurobehavioral performance impairment irrespective of daily sleep ration in these experiments.

DISCUSSION

This study evaluated the waking neurobehavioral and sleep physiological effects of chronic sleep restriction in healthy young adults using random assignment to dosages of sleep maintained over 14 consecutive days under continuous behavioral, physiological and medical monitoring. Such continuous laboratory control of subjects' sleep-wake times,
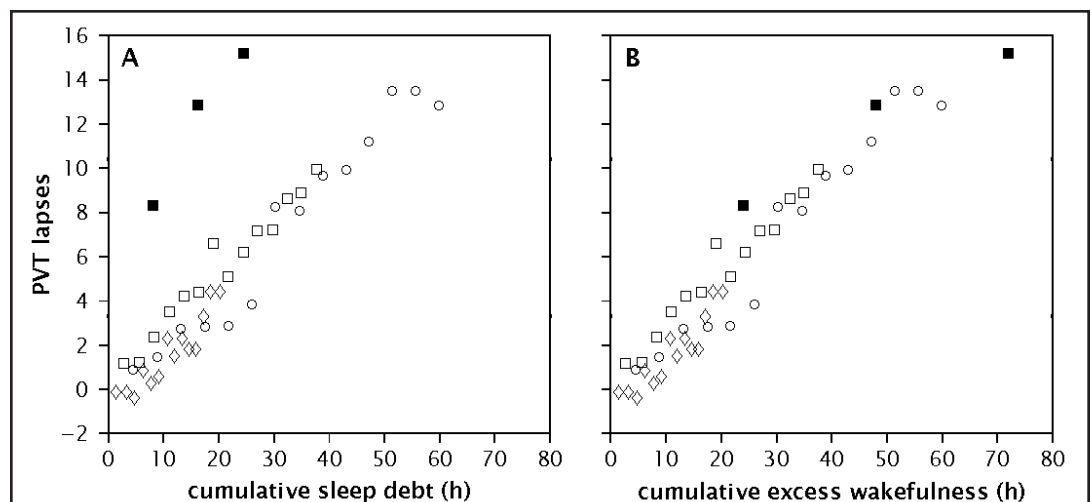

Figure 4—Behavioral alertness as a function of cumulative sleep debt versus cumulative excess wakefulness. The panels show behavioral alertness, as measured by psychomotor vigilance task performance lapses (relative to baseline), plotted as a function of cumulative sleep debt (panel A) and as a function of cumulative excess wakefulness (panel B). Cumulative hours of sleep debt (panel A) were determined relative to the statistically estimated subject-specific daily sleep need of 8.16 ± 0.73 h (mean $\pm$ s.e.). For an average individual, this is the cumulative time of sleep reduction below 8.16 h per day. Cumulative hours of excess wakefulness (panel B) were calculated as those hours in which wakefulness exceeded the statistically estimated subject-specific critical wake period of 15.84 ± 0.73 h (mean $\pm$ s.e.). For an average individual, this is the cumulative time of wakefulness in excess of 15.84 h per wake period. Each point represents the average for a day (across 14 days of sleep restriction and 3 days of total sleep deprivation) for subjects randomized to the 8 h ($\diamond$), 6 h ($\square$), 4 h ($\bigcirc$) and 0 h ($\blacksquare$) sleep period conditions. Panel A shows that from the perspective of sleep debt, the response to the 0 h sleep condition (total sleep deprivation) is fundamentally different from the response to the 8 h, 6 h and 4 h sleep period conditions (chronic sleep restriction). However, panel B reveals that these two experimental paradigms can be described by a single near-linear model when focusing on the cumulative time of excess wakefulness. This difference in perspective affects the position of the data points for the 0 h sleep condition: Subjects who received 0 h sleep each day built up a statistically estimated average sleep debt of only 8.16 h of sleep per day, but extended their consecutive wakefulness by 24 h per day. Thus, panel B illustrates the monotonic, near-proportional relationship between cumulative excess wakefulness and neurobehavioral performance impairment irrespective of daily sleep ration.

activities and assessments sets this experiment apart from previous published reports on the effects of prolonged chronic sleep restriction (i.e., more than a week). Contrary to earlier, uncontrolled studies of prolonged sleep restriction, this experiment yielded convergent findings of sleep dose-response effects on all three cognitive performance functions. Sleep periods chronically limited to 4 h and 6 h per night progressively eroded the effectiveness of psychomotor vigilance performance, working memory performance and cognitive throughout performance, providing convergent evidence for the adverse effects of chronic sleep restriction on cognitive functions. These results confirm and substantially extend those obtained in earlier laboratory-controlled studies of chronic sleep restriction between 4 h and 6 h per night for up to 7 days.[10,15] Claims that humans adapt to chronic sleep restriction within a few days, on the other hand, are not supported by the present findings.

Since chronic restriction of sleep between 4 h and 6 h per night for 14 days produced cognitive performance deficits comparable to those found under conditions of 1 to 2 days of total sleep deprivation (Figure 1), it appears that even relatively moderate sleep restriction—if sustained night after night—can seriously impair waking neurobehavioral functions in healthy young adults. This conclusion is reinforced by four additional observations: (1) The sensitivity of waking cognitive performance functions to chronic sleep restriction was found both between conditions (i.e., impact of 4 h versus 6 h versus 8 h nightly sleep periods) and within subjects (i.e., impact of increasing days in condition); (2) The effects of chronic sleep restriction were not limited to a few times of day, but rather they were evident in performance throughout the waking day (each point in the cognitive performance data shown in Figure 1 reflects the average daily performance on each task for assessments taken during the 16 h between 07:30 and 23:30); (3) Mixed-effects regression models were used to quantify the waking neurobehavioral responses to chronic sleep restriction while taking into account inter-individual variability in these responses (ensuring that all statistical analyses and the curves in Figure 1 are representative of the subject population's responses to condition); and (4) The cumulative cognitive deficits are not likely to be due to boredom, monotony, non-compliance, or any other non-sleep-related hypothetical construct, since subjects in the 8 h control condition showed no significant progressive deficits (and displayed continued learning on the working memory and cognitive throughput tasks) despite being exposed to the same degree of laboratory control, experimental procedures, and repeated testing.

We conclude that the effects of sleep chronically limited to 4 h and 6 h per night on cognitive performance appear to reflect progressive neurocognitive dysfunction in systems underlying sustained attention and working memory. They implicate an as yet unknown neurobiological process that is sensitive to sleep duration over consecutive days. There has been little basic research published on possible mechanisms for the effects of chronic sleep loss on waking cognitive performance, but recently it has been proposed that an increase in A_1 adenosine receptors in the basal forebrain in response to initial sleep loss may sensitize the brain to subsequent sleep loss.[31] Whatever the mechanism, it is parsimonious to suggest that the same process underlies the progressive performance degradation we observed on all three cognitive tasks (Figures 1A, 1C, 1D). Elsewhere, we have suggested that this process may be characterized as wake state instability.[21] Those seeking to identify the neurobiological basis of cumulative cognitive deficits engendered by chronic sleep restriction will have to explain how the brain can be increasingly affected for a period of at least 14 consecutive days.

The participants in our experiments were healthy younger adults, 21–38 years of age. This is the age range commonly found in occupations associated with chronic sleep restriction (e.g., shift workers, military personnel, medical and surgical residents). Many factors—such as the added responsibilities of rearing young children, or the desire to obtain additional income—contribute to lifestyles that result in chronic sleep restriction. Younger adults are often assumed to be better able to cope with the demands of prolonged wakefulness and lifestyles that lead to chronic sleep loss. It is of concern then that our results revealed the

development of cumulative neurobehavioral performance deficits when young adults were chronically restricted to 4 h and 6 h nocturnal sleep. It is likely that such deficits would also be found in younger subjects (e.g., adolescents[32]) and older individuals. We do not know if the same degree of cumulative impairment occurs across the continuum of habitually short to habitually long sleepers, among those sleeping at different circadian times (e.g., night shift workers), and in females compared to males. Additional investigations are underway to address some of these issues.

Chronic restriction of sleep to 4 h and 6 h initially elevated subjective sleepiness ratings on both the Stanford Sleepiness Scale and the Karolinska Sleepiness Scale, but as sleep restriction continued, there were only minor further increases in these ratings (Figure 1B). In fact, unlike PVT and DSST performance functions (Figures 1A, 1C), sleepiness ratings never reached levels equivalent to those found after 2 nights of total sleep deprivation. Surprisingly, by the end of the 14 days of sleep restriction, when performance was at its worst levels, subjects in the 4 h and 6 h sleep period conditions reported feeling only slightly sleepy. Therefore, unlike performance measures, sleepiness ratings appeared to show adaptation to chronic partial sleep deprivation. In addition, there were no significant differences in sleepiness scores between the 4 h and 6 h sleep period conditions. It is unlikely that this was the result of a ceiling effect or other metric-related artifact, because subjects in the total sleep deprivation condition reported considerably greater levels of sleepiness, and did not show evidence of adaptation.

These findings for subjective sleepiness suggest that once sleep restriction is chronic, subjects either cannot reliably introspect with regard to their actual sleepiness levels, or as long as they are receiving at least approximately 4 h of sleep nightly they do not experience a sense of sleepiness anywhere near the levels found for total sleep deprivation. Regardless of the explanation, the lack of reports of intense feelings of sleepiness during chronic sleep restriction may explain why sleep restriction is widely practiced—people have the subjective impression they have adapted to it because they do not feel particularly sleepy. More research will be needed to identify the factors that shape subjects' perceptions of their sleepiness during chronic sleep restriction.

Measures of sleep physiology were less responsive to chronic sleep restriction than were waking neurobehavioral functions. The primary effects on sleep architecture were immediate, overall reductions in the amounts of stages 1, 2 and REM sleep (Figures 2B, 2C, 2E). SWS and δ power in the non-REM sleep EEG were conserved among conditions (Figures 2D, 2F). A recent sleep restriction study of within-subjects, non-counterbalanced design reported that when analyzing sleep over a standardized period common to two different study conditions, SWS and δ power (or slow-wave activity; SWA) in restricted sleep (4 h TIB) were greater than SWS and SWA in the first part of extended sleep (12 h TIB).[33] In the present study, there were no statistically significant differences for SWS and SWA among the three sleep restriction conditions when analyzing sleep architecture over the first 4 h of each sleep period.[34]

The conservation of SWS and SWA among all three sleep restriction conditions relative to the marked development of cognitive performance deficits in the 4 h and 6 h sleep restriction conditions is inconsistent with the "core sleep" hypothesis,[6,7] which asserts that "core" or "obligatory" sleep occupies the first part of the night and serves to "repair the effects of waking wear and tear on the cerebrum" (ref. 7, p. 57). In the core sleep hypothesis, all sleep obtained beyond this core sleep duration is considered to be "optional" or "facultative" sleep, which "fills the tedious hours of darkness until sunrise" (ref. 7, p. 57). According to this hypothesis, only core sleep—especially that dominated by SWS and SWA—is required for adequate daytime functioning to be maintained. Considering that SWS and SWA were conserved among sleep restriction conditions in the present study, the finding that cumulative cognitive impairment developed in cerebral functions at 4 h and 6 h time for sleep per night indicates that the current threshold of 6 h for core sleep duration (see ref. 8) cannot be correct. If 6 h sleep per day were the maxi-

mum duration of sleep required to maintain normal cerebral functions, cumulative cognitive performance deficits should not have developed in that condition. Thus, the results from the present study do not support a functional distinction between "core" and "optional" sleep.

Regardless of which physiological measure of sleep is theorized to reflect homeostatic sleep drive, there was scant evidence that homeostatic sleep drive accumulated across days of sleep restriction. Sleep architecture variables did not show any substantial, consistent cumulative changes across the 14 days of sleep restriction in the 4 h and 6 h sleep period conditions. There appeared to be no significant cumulative pressure for non-REM sleep, and only minor cumulative changes in REM pressure, as sleep restriction continued. Power spectral analysis showed that δ power in the non-REM sleep EEG, which is a putative marker of homeostatic sleep drive,[17] increased only modestly over the first few days of sleep restriction, and thereafter displayed negligible further increases (Figure 2F). This was not due to limited brain capacity for generating δ power, since the δ power response to total sleep deprivation was much greater (Figure 2F).

The modest increase observed in δ power during sleep restriction is consistent with previous work,[35] and with mathematical simulations we ran using the two-process model of sleep regulation[17] which predicted that the average level of homeostatic sleep drive across days of sleep restriction would show an acute sleep dose-dependent change followed by stabilization within 3 days. Even though the sleep physiological responses to both chronic sleep restriction and total sleep deprivation were consistent with contemporary model-based theory for the regulation of sleep,[17] it is remarkable that the changes in cognitive performance functions over days of sleep restriction (Figures 1A, 1C, 1D) were not matched by progressive changes in sleep architecture over days (Figure 2F). This means that the common implicit assumption that momentaneous homeostatic sleep drive is indicative of concurrent waking performance capability must be put to rest (see also ref. 36). It appears that the concept of homeostatic sleep drive cannot account for the cumulative neurobehavioral performance changes observed across consecutive days of sleep restriction.

We evaluated whether the neurobehavioral effects observed with chronic sleep restriction could be explained by cumulative total sleep loss, which we refer to here as the "sleep debt" hypothesis.[5] Psychomotor vigilance lapses were used as the primary neurobehavioral metric for this evaluation because PVT lapses displayed no learning curve and no significant cumulative impairment in the 8 h sleep period condition. PVT lapses showed evidence of decreased behavioral alertness as a sleep dose-dependent, near-linear function of the number of days in the 6 h, 4 h and 0 h sleep period conditions (Figure 1A). This would seem to suggest that the development of neurobehavioral performance deficits over days of sleep restriction could be accounted for solely by sleep debt (i.e., the cumulative loss of time for sleep) regardless of homeostatic sleep drive. On the other hand, the sleep debt hypothesis would predict that the highest level of psychomotor vigilance performance impairment should be observed during days 7–14 in the 4 h sleep period condition, when the cumulative reduction of sleep time was greater in this condition than in any of the other experimental conditions (Figure 3B). Even after 14 days, however, the performance deficits in the 4 h sleep period condition did not exceed those observed after 3 days in the 0 h sleep period condition (Figure 1A). Thus, the cumulative reduction of time for sleep cannot by itself explain the profiles of waking performance impairment in all four experimental conditions (Figure 4A).

In introducing a new hypothesis, we postulated that the build-up of neurobehavioral deficits was not caused by reduction of sleep time *per se*, but rather by excessive wakefulness beyond a maximum period during which stable neurobehavioral functioning could be maintained. When we defined "excess wakefulness" as all waking time beyond this hypothetical critical period, behavioral alertness measured by performance lapses was a near-linear function of excess wakefulness across days of sleep restriction for all four experimental conditions (Figure 4B). This suggests that cumulative wake extension (i.e., excess wakefulness),

rather than cumulative loss of sleep (i.e., sleep debt), is the primary cause of progressively reduced behavioral alertness both across days of chronic sleep restriction and across days of total sleep deprivation (cf. Figures 4A and 4B). Subjects in all four experimental conditions appeared to experience the same cumulative "cost" (i.e., increase in lapses of behavioral alertness) for each consecutive hour they extended their wake periods (near-linear relationship displayed in Figure 4B).

With mixed-effects regression modeling[27] of the psychomotor vigilance performance data, the critical wake period beyond which lapsing would be expected to increase was statistically estimated to be 15.84 ± 0.73 h (mean ± s.e.). For the average healthy young adult in the experiments, limiting daily wakefulness to this level would be expected to prevent the build-up of neurobehavioral deficits over days. Accordingly, per 24 h day, the average value for human sleep need to prevent cumulative neurobehavioral deficits would appear to be 8.16 h. Although we found no evidence that subjects had any significant neurobehavioral impairment at the beginning of sleep restriction, it is possible that the 8 h baseline sleep periods were not sufficiently long to completely prevent the build-up of neurobehavioral impairment. Given that all subjects underwent the same baseline procedures regardless of experimental condition, and since neurobehavioral performance measures were expressed relative to baseline (Figure 1), any neurobehavioral deficits present at the beginning of sleep deprivation should not have affected the statistical evaluation of the results reported here. Yet, it is noteworthy that future studies of sleep or sleep deprivation could benefit from extending baseline sleep periods to more than 8 h time in bed per day.

We found that the statistically estimated duration of the critical waking period varied greatly among the 48 young adults in our experiments. Large inter-individual variability has also been reported for the duration of nocturnal sleep in adult populations.[3,37] We observed a positive correlation between average sleep duration in the 5 days prior to the experiment and the rate of change in behavioral alertness during the 14 days of sleep restriction, suggesting that those subjects who habitually slept longest tended to be more affected by the 14 days of sleep restriction. This correlation was modest, however, suggesting that other factors may also contribute to inter-individual differences in the neurobehavioral responses to chronic sleep restriction.[8,38]

The physiologic expression of sleep in humans appears to have multiple functions, ranging from metabolic[39] to neurocognitive.[40] Chronic loss of physiological sleep has been documented to adversely affect endocrine function,[39] cardiovascular events,[41] and other health-related outcomes.[37] Yet, it has remained unclear why *homo sapiens* should invest so much time in sleep—roughly one-third of every day in adults—to fulfill the various physiological, cognitive and health-related functions that sleep may have. It is well established that the temporal regulation of sleep is governed by an interplay of homeostatic and circadian processes.[17,42–44] The present data suggest that this temporal regulation of sleep serves to protect human neurobehavioral functions from degradation due to excessive wakefulness within and between circadian cycles.

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