Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion

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[1]*Sleep Research and Treatment Center, Department of Psychiatry;* [2]*Health Evaluation Sciences, Penn State College of Medicine, Hershey, Pennsylvania;* [3]*Reproductive Biology and Medicine Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; and* [4]*First Department of Pediatrics and Unit on Endocrinology, Metabolism, and Diabetes, Athens University Medical School, Athens, Greece*

Vgontzas AN, Pejovic S, Zoumakis E, Lin H-M, Bixler EO, Basta M, Fang J, Sarrigiannidis A, Chrousos GP. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. *Am J Physiol Endocrinol Metab* 292: E253–E261, 2007. First published August 29, 2006; doi:10.1152/ajpendo.00651.2005.—Sleep loss has been associated with increased sleepiness, decreased performance, elevations in inflammatory cytokines, and insulin resistance. Daytime napping has been promoted as a countermeasure to sleep loss. To assess the effects of a 2-h midafternoon nap following a night of sleep loss on postnap sleepiness, performance, cortisol, and IL-6, 41 young healthy individuals (20 men, 21 women) participated in a 7-day sleep deprivation experiment (4 consecutive nights followed by a night of sleep loss and 2 recovery nights). One-half of the subjects were randomly assigned to take a midafternoon nap (1400–1600) the day following the night of total sleep loss. Serial 24-h blood sampling, multiple sleep latency test (MSLT), subjective levels of sleepiness, and psychomotor vigilance task (PVT) were completed on the fourth (predeprivation) and sixth days (postdeprivation). During the nap, subjects had a significant drop in cortisol and IL-6 levels ($P < 0.05$). After the nap they experienced significantly less sleepiness (MSLT and subjective, $P < 0.05$) and a smaller improvement on the PVT ($P < 0.1$). At that time, they had a significant transient increase in their cortisol levels ($P < 0.05$). In contrast, the levels of IL-6 tended to remain decreased for ~8 h ($P = 0.1$). We conclude that a 2-h midafternoon nap improves alertness, and to a lesser degree performance, and reverses the effects of one night of sleep loss on cortisol and IL-6. The redistribution of cortisol secretion and the prolonged suppression of IL-6 secretion are beneficial, as they improve alertness and performance.

alertness; sleep deprivation; proinflammatory cytokines; hypothalamic-pituitary-adrenal axis; daytime sleep

ACUTE SLEEP LOSS, either total or partial, is associated with increased sleepiness and decrements in neurobehavioral performance (24, 29). Also, more recently it has been shown that sleep loss is associated with next-day increase of proinflammatory cytokines, e.g., IL-6 and TNF-α (10, 31, 34), which have been proposed as mediators of pathological or experimentally induced sleepiness in humans and have been shown to be associated with an unfavorable metabolic profile, a higher risk of cardiovascular adverse events, and decreased longevity (10, 23).

Napping and/or use of wake-promoting compounds, i.e., caffeine, have been used by millions of humans whose sleep is restricted by occupational or social demands. Although it is widely acknowledged that adequate sleep is necessary not only for optimal waking function but also to promote good health, longevity, and well-being, few studies have documented the favorable effect of napping on neurobehavioral deficits associated with sleep loss (7, 24, 26). The effects of postdeprivation napping during the nap and the subsequent postnap period on circulating levels of cortisol and on somnogenic proinflammatory cytokines have not been studied as yet. Cortisol is the end product of the hypothalamic-pituitary-adrenal (HPA) axis, and its endogenous release is regulated by corticotropin-releasing hormone (CRH), produced by and released from the paraventicular nucleus and corticotropin (ACTH) released from the pituitary. Both CRH and ACTH induce increased waking, whereas increased endogenous levels of cortisol in humans have been associated with increased arousal and sleep disruption (9, 28, 37).

The goal of this study was to assess the effects of a 2-h midafternoon nap on sleepiness measured with the multiple sleep latency test (MSLT), performance measured with a psychomotor vigilance test (PVT), and plasma levels of cortisol, IL-6, TNF-α, and tumor necrosis factor receptor 1 (TNFR1), serially measured every half-hour in 41 young, healthy men and women after a night of total sleep loss. A 2-h nap was chosen so that the subjects were given the opportunity to sleep for a full sleep cycle, whereas midafternoon was chosen because it coincides with the peak of daytime sleepiness in humans (15) and the postlunch rest period for most workers. We hypothesized that daytime napping would be associated with an improvement of alertness and performance and that this improvement could be associated with an increase of arousal-promoting hormones, i.e., cortisol, and a decrease of sleepiness-mediating inflammatory cytokines, such as IL-6 and TNF-α. A secondary objective was to test for possible sex differences in terms of postdeprivation napping effects on behavioral and hormonal measures.

MATERIALS AND METHODS

Subjects

Forty-one normal sleepers (20 men, 21 women) 18–30 yr of age were recruited from the community and from the medical and tech-

nical staff and students of Milton Hershey Medical Center. They were in good general health and physically active but not excessively so. Specifically, the subjects that were jogging >45 miles/wk were excluded from the study because of potential effects on the HPA axis (17). They had no sleep complaints or circadian abnormalities, were not taking any medications, and were screened in the laboratory for sleep-disordered breathing, nocturnal myoclonus, or other primary sleep disorders. Also, a battery of clinical tests (including a complete cell blood count, urinalysis, thyroid indexes, electrocardiogram, and urine screen for drug use) were negative for abnormal findings. Subjects were randomly assigned to take a midafternoon nap or not the day following the night of total sleep loss. Men and women were equally distributed in the two groups ("nap" vs. "no-nap" group). The two groups were very similar in terms of age and body mass index (23.4 ± 0.6 vs. 23.1 ± 0.7 yr and 23.7 ± 0.6 vs. 23.9 ± 0.5 kg/m²).

Protocol

Each subject participated in a sleep deprivation experiment that lasted 7 days. Adequate sleep time and regular sleep schedules were verified with a sleep log and actigraphy for 2 wk before the study. After four consecutive nights in the sleep laboratory (1 adaptation and 3 baseline nights), the subjects were deprived of sleep during the entire fifth night, whereas they were allowed to sleep again on *nights 6 and 7* (recovery nights; Table 1). The subjects stayed awake in the presence of nursing or technical staff, and total wake time before the first recovery night was 40 h. One-half of the subjects were randomly assigned to take a midafternoon nap (1400–1600) the day following the night of total sleep loss. Twenty-four-hour blood sampling was performed serially every 30 min on the fourth day and night (predeprivation) and on the sixth day (the day following sleep deprivation) and the recovery night. In women, both periods of blood sampling took place during the follicular phase, as evidenced by low progesterone levels obtained on the fourth and sixth days of experiment. An indwelling catheter was inserted in the antecubital vein ~30 min before the first blood sample. The catheter was kept patent with small amounts of heparin (the total amount of heparin did not exceed 800 U/24-h period). During the sleep recording period, blood was collected outside the subjects' room through a perforation in the wall via extra tubing to decrease sleep disturbance from the blood sampling technique. During the night of sleep deprivation, as well as throughout the entire sampling period, the subjects were ambulatory, allowed to watch television, play computer and table games, go to the bathroom, etc. Also, they were instructed not to change their diet, and their three daily meals were at about 0700, 1200, and 1800. However, there was no count of caloric intake or food composition. The brightness of the light in the room in which the blood drawing took place was, on average, ~800 lux, ranging from a minimum of 200 to a maximum of 1400 lux (Minolta III F digital light meter; Konica, Minolta, Tokyo, Japan). The protocol was approved by the Institutional Review Board, and each subject signed a written consent form.

Sleep Recordings

Assessment of nighttime and nap sleep. Sleep laboratory recordings were carried out in a sound-attenuated, light- and temperature-controlled room that had a comfortable bedroom-like atmosphere. Each subject was monitored with EEG, electrooculograph, and electromyography recordings continuously for 8 h (2230–0630). The sleep schedule in the laboratory at baseline was similar to the subjects' normal sleep schedule. Specifically, the subjects' habitual times to go to bed and rise in the morning were no different than by an hour from their sleep schedule in the laboratory. Also, total sleep duration the week before the study, based on sleep log and actigraphy, was 7.4 ± 0.1 and 7.8 ± 0.1 h, respectively. The subjects who were allowed to take a postdeprivation nap were recorded for 2 h between 1400 and 1600. Polysomnographic recordings were obtained and scored in accordance with standard methods (20). Sleep parameters were assessed as previously described (31).

Assessment of Daytime Sleepiness and Performance

MSLT. During the fourth and sixth days (days of blood sampling) the subjects' levels of sleepiness and alertness were evaluated using MSLT (22). In our study, we allowed six 20-min opportunities to sleep, at 0900, 1200, 1500, 1700, 1900, and 2100. Polysomnographic methods were used to determine whether the subject fell asleep. Onset of sleep was defined as attaining any sleep stage for a duration of one epoch (30 s) or longer. The MSLT was terminated 20 min after lights-out if there had been no sleep or after two consecutive epochs of Stage 2.

Subjective levels of sleepiness. These were assessed using a 10-cm visual analog scale that ranged from 0 (not sleepy at all) to 10 (extremely sleepy) and the Stanford Sleepiness Scale (a 7-point question: "how sleepy do you feel right now?") (13), which were administered every hour.

PVT. The PVT is a test of behavioral alertness, and it involves a simple reaction time (RT) test designed to evaluate the ability to sustain attention and respond in a timely manner to salient signals (29). The primary variables assessed in our study were *1*) frequency of lapses, which refers to the number of times the subject failed to respond to the signal or failed to respond in a timely manner (>500 ms); *2*) duration of lapse domain, which refers to the shifts in lapse duration calculated from the 10% slowest RTs, a metric that reflects vigilance response slowing; *3*) optimum reaction times, which are the averages of the 10% fastest RTs per trial and reflect the very best performance an operator is capable of producing; and *4*) the median RT in the trial. Each PVT trial lasted for 10 min, and each subject had three practice trials within an hour the night before the next day's testing. In this study, PVT was administered every hour from 0800 to 2200 during the fourth and sixth days.

Hormone and Cytokine Assays

Blood collected from the indwelling catheter was transferred to an EDTA-containing tube and refrigerated until centrifugation (within 3 h). The plasma was frozen at −70°C until assay. Cortisol levels were measured by specific radioimmunoassay techniques, and plasma TNF-α and IL-6 were measured by ELISA (R&D Systems, Minneapolis, MN) as previously described (31, 34). The lower limit of detection for cortisol was 0.7 μg/dl, and the intra- and interassay coefficients of variation were, respectively, 4.6 and 6.0%. The intra- and interassay coefficients of variation ranged from 5.6 to 6.1 and 7.5 to 10.4%, respectively, for TNF-α, from 3.6 to 5.0 and 3.7 to 8.8% for TNFR1, and from 3.2 to 8.5 and 3.5 to 8.7% for IL-6. The lower detection limits for TNF-α, TNFR1, and IL-6 were 0.18, 7.8, and 0.094 pg/ml, respectively.

Table 1. *Sleep deprivation: nap protocol in young men and women*

| | Days | | | | | | |
| | Baseline | | | Sleep Loss | | Recovery | |
	1	2	3	4	5	6	7
Sleep lab							
Nighttime	x	x	x	x		x	x
MSLT				x		x	
Subjective sleepiness				x		x	
PVT				x		x	
2-h nap* (1400–1600)						x	
Blood drawing				x		x	

*50% of the subjects completed the 2-h nap. MSLT, multiple sleep latency test; PVT, psychomotor vigilance test.

Statistical Analyses

In this study, we performed two types of comparisons with the objectives of assessing the effects of sleep deprivation and postdeprivation 2-h nap, respectively. The first was to compare the differences of daytime and nighttime sleep outcomes before and after sleep deprivation in each nap group. Specifically, we compared differences in sleep of *night 6* (recovery night) minus the average of *nights 2* and *3* (baseline) using paired *t*-tests. The second was to compare the differences in hormonal levels and sleep outcomes (pre- minus postdeprivation) between the nap and no-nap groups before, during, and after the 2-h nap period. We used analysis of covariance (ANCOVA) to adjust for the baseline (predeprivation) hormone values and baseline percent sleep time. Specifically, to assess the effects of the postdeprivation 2-h nap on hormonal values, we compared the differences in the change of hormonal values before and after sleep loss between the nap vs. no-nap groups for the nap (1400–1600) and the postnap periods (1600–2230), respectively. Significance of gender effects and its interaction with the nap condition were also tested. Similar analyses contrasting the difference in the change in MSLT values as well as PVT values after sleep loss before (0900–1400) and after the nap (1700–2100) periods were performed. MSLT data are presented with sleep onset defined as the presence of any stage of sleep for a duration of one epoch (30 s). Four PVT variables were included in the PVT analysis: number of lapses (i.e., RTs ≥ 500 ms) transformed by [$\sqrt{x} + \sqrt{(x+1)}$]; duration of lapse domain (i.e., mean 1/RT from slowest 10% RTs per trial); optimum reaction times (i.e., mean of the 10% fastest RTs per trial); and median RT (31). To assess the sleep homeostatic response following sleep deprivation, we compared differences in SWS and rapid eye movement (REM) sleep in the recovery sleep (*night 6* for the no-nap group; *night 6* plus nap for the nap group) minus the baseline sleep between the two groups. Last, a two-sample *t*-test was used to compare the gender effects for sleep of daytime nap following sleep deprivation.

Fast Fourier Transform (FFT) was performed with software developed by our group on all polysomnographic recordings of *nights 2, 3,* and *6* and the nap sleep. The analysis was performed using the C3-A1 channel on 30-s epochs with a Hanning-type window. The window had a size of 256 samples and a length of 2.56 s. This produced 15 windows per epoch with 60 overlapping samples between successive windows. The frequency resolution was 0.39 Hz. A 0.4- to 3.9-Hz band for Δ and a 4.0- to 7.0-Hz band for Θ was used. The results of the FFT were averaged during non-REM sleep for further statistical analyses.

Data are presented as means $\pm$ SE for the purpose of group comparisons, except for demographic data and anthropometric data (age and body mass index), for which we used SD to describe variance.

RESULTS

Sleep Pre- and Postdeprivation in Nap vs. No-Nap Groups

Subjects in the no-nap group demonstrated significantly shorter sleep latencies (SL) and increased percentage of total sleep time (ST) in the postdeprivation than the baseline nights (differences: 11.70 ± 2.7 min SL; $-2.58 \pm 1.2\%$ ST, both $P < 0.05$). Also, they experienced a higher percentage of SWS and lower percentage of Stage 1 and Stage 2 sleep during the postdeprivation night compared with baseline nights (differences: $-8.17 \pm 1.1\%$ SWS; $1.19 \pm 0.4\%$ Stage 1; $6.41 \pm 1.4\%$ Stage 2, all $P < 0.05$; Table 2).

Subjects in the nap group demonstrated significantly shorter SL (difference: 11.33 ± 5.5 min, $P < 0.05$) on postdeprivation night (*night 6*) compared with baseline nights (average of *nights 2* and *3*). In terms of sleep stages, only the percentage of

Table 2. *Nighttime sleep pre- and postdeprivation in 21 young females and males (no-nap group)*

	Nights 2–3	Night 6
SL, min	19.7±2.4	8.0±1.5[a]
WTASO, min	25.8±3.8	24.9±4.9
%ST	90.9±1.0	93.5±1.1[a]
%Stage 1	5.0±0.6	3.8±0.7[a]
%Stage 2	60.0±1.5	53.5±1.8[a]
%Stage 3	7.7±0.7	10.4±0.9[a]
Stage 3, min	33.9±2.9	46.5±3.8[a]
%Stage 4	4.9±0.9	10.4±1.8[a]
Stage 4, min	21.6±4.0	47.0±8.1[a]
%SWS	12.6±1.1	20.8±1.6[a]
SWS, min	55.5±5.1	93.4±7.0[a]
%REM	22.5±1.1	21.9±1.2
REM, min	98.4±5.0	98.8±5.5
REM latency, min	92.0±6.1	90.6±10.0

Data represent means $\pm$ SE. SL, sleep latency; WTASO, wake time after sleep onset; %ST, %sleep time; SWS, slow-wave sleep; REM, rapid eye movement sleep. [a]$P < 0.05$.

REM sleep was significantly increased ($P < 0.05$), whereas REM latency was significantly shorter postdeprivation than predeprivation (differences: $-2.89 \pm 1.3\%$ REM; 19.94 ± 10.0 min, both $P < 0.05$; Table 3). In contrast to the no-nap group, SWS was similar between baseline and recovery night. No sex differences were present either in the no-nap or the nap group in terms of the effects of sleep deprivation on sleep.

Sleep of Daytime Nap Following Sleep Deprivation

Table 4 shows the amount and structure of daytime sleep after sleep deprivation. As expected, SWS was the predominant sleep stage compared with other sleep stages. Specifically, subjects spent 46.1% in SWS, 37.4% in Stage 2 sleep, and 13.6% in REM sleep. No gender effects were observed.

SWS and REM Sleep in Recovery Sleep in Nap vs. No-Nap Groups

The sum of the increase of SWS during the nap and postnap night in the nap group was borderline significantly higher compared with that on the recovery night in the no-nap group ($P = 0.056$). Stage 4 sleep remained the same between the two groups, whereas Stage 3 sleep tended to be higher in the nap

Table 3. *Nighttime sleep pre- and postdeprivation in 20 young females and males (nap group)*

	Nights 2–3	Night 6
SL, min	28.7±5.2	17.4±3.8[a]
WTASO, min	26.4±3.9	35.7±6.1
%ST	88.8±1.39	89.3±1.2
%Stage 1	4.7±0.7	4.2±0.7
%Stage 2	58.9±1.3	57.0±1.2
%Stage 3	8.4±0.7	8.9±0.7
Stage 3, min	35.7±3.0	38.5±3.1
%Stage 4	5.3±1.1	4.3±1.3
Stage 4, min	22.6±5.0	18.2±5.4
%SWS	13.6±1.2	13.2±1.2
SWS, min	58.3±5.4	56.7±5.2
%REM	22.8±1.1	25.7±1.4[a]
REM, min	97.8±5.4	111.3±6.8
REM latency, min	88.6±6.9	68.6±5.8[a]

Data represent means $\pm$ SE. [a]$P < 0.05$.

group than in the no-nap group ($P < 0.1$). In addition, the sum of REM sleep in the nap and postnap sleep was significantly increased compared with baseline in the nap group, whereas there was no difference in the no-nap group (Table 5).

FFT Analysis

Subjects in the no-nap group demonstrated a significant increase in the total amount of Δ and Θ power during non-REM sleep on postdeprivation night compared with baseline ($31.0 \pm 8.6\%$ increase for Δ power and $26.2 \pm 6.3\%$ increase for Θ power, both $P < 0.01$).

Similarly, in the nap group, subjects demonstrated a significant increase in the total amount of Δ power during non-REM sleep on the postdeprivation nap and night compared with baseline ($31.0 \pm 10.1\%$, $P < 0.01$). There was also a significant increase in Θ power on the postdeprivation nap plus night compared with baseline ($37.1 \pm 6.6\%$, $P < 0.01$). The largest increases of Δ and Θ power per epoch were observed during the nap sleep (60.0 ± 11.7 and $47.0 \pm 6.9\%$ increases, respectively compared with baseline, $P < 0.01$). However, in the nap group, in contrast to the no-nap group, there was a significant decrease of Δ power ($-18.0 \pm 7.9\%$, $P < 0.05$) during the recovery night compared with baseline.

No sex differences were observed in either the nap or the no-nap group in terms of the effects of sleep deprivation on delta and theta power.

Daytime Sleepiness and Performance

MSLT. After one night of total sleep loss, subjects in both the no-nap and nap groups had significantly shorter SLs compared with baseline [differences of the mean MSLT values (postdeprivation minus baseline) in the prenap period within each group: -10.05 ± 0.3 min in the no-nap group, -9.55 ± 0.3 min in the nap group, both $P < 0.01$]. Postdeprivation sleepiness was similar between the two groups (difference of the differences between no-nap and nap groups, in the prenap period 0.51 ± 0.4 min, $P = 0.23$). However, after the midafternoon nap, subjects in the nap condition experienced significantly less sleepiness than subjects who did not nap following the night of total sleep loss in the same time period (1700–2200) [difference of the mean MSLT values (postdeprivation minus baseline) in the postnap period within each group;

Table 4. *Nap sleep (1400–1600) postdeprivation in 20 young females and males*

	2-h Nap Sleep
SL, min	3.3 ± 0.7
WTASO, min	4.5 ± 2.1
%ST	93.6 ± 2.1
%Stage 1	2.9 ± 0.8
%Stage 2	37.4 ± 2.0
%Stage 3	16.5 ± 2.2
Stage 3, min	18.6 ± 2.7
%Stage 4	29.6 ± 3.7
Stage 4, min	34.1 ± 4.4
%SWS	46.1 ± 2.8
SWS, min	52.7 ± 3.8
%REM	13.6 ± 2.7
REM, min	15.2 ± 2.9
REM latency, min	56.5 ± 5.6

Data represent means $\pm$ SE.

Table 5. *Comparison of change of amount of SWS and REM sleep between baseline and recovery sleep in young men and women in no-nap and nap conditions*

Recovery Sleep - Baseline Sleep	No-Nap Condition ($n = 21$)	Nap Condition* ($n = 20$)
Stage 3, min	12.0 ± 4.0	22.0 ± 4.1
Stage 4, min	25.5 ± 5.7	29.5 ± 5.9
SWS, min	37.7 ± 4.8	51.3 ± 4.9^{b}
REM, min	0.5 ± 5.7	28.5 ± 5.8^{a}

Data represent means $\pm$ SE. *SWS and REM sleep were based on the sum of these stages for postdeprivation nap and recovery night (total of 10 h of sleep recording). [a]$P < 0.05$; [b]$P = 0.056$.

-11.8 ± 0.9 min in the no-nap group; -4.6 ± 0.9 min in the nap group; difference of the differences of the mean MSLT values in the postnap period between the two groups was 7.3 ± 1.6 min, $P < 0.01$; Fig. 1].

Subjective sleepiness. Subjective sleepiness, measured with the visual-analog scale and the Stanford Sleepiness Scale in the postnap period (1700–2200), showed a trend toward improvement in the nap group compared with the no-nap group (differences: -1.1 ± 0.7, $P = 0.1$ for the visual-analog scale, and 0.7 ± 0.4, $P < 0.1$ for the Stanford sleepiness scale). This trend reached significance for the Stanford Sleepiness Scale in the late postnap period (2000–2200; difference of 0.9 ± 0.4, $P < 0.05$).

PVT. Analyses of performance data in the postnap period showed a marginal improvement in the nap group compared with the no-nap group in two variables (number of lapses and slowest 10% RTs per trial), whereas there was no difference in the fastest 10% RTs per trial and median RT. Specifically, RT in the transformed 10% slowest responses tended to improve by 0.3 s ($P = 0.06$), and transformed number of lapses tended to be reduced by 1.2 ($P < 0.06$).

Effects of Napping on Hormonal/Cytokine Secretion

Cortisol. Daytime napping following a night of total sleep loss affected cortisol secretion significantly during both the nap and postnap periods. Specifically, cortisol levels were significantly lower during the nap [between-group difference, nap vs. no-nap of the change in cortisol levels before and after sleep loss was -3.3 ± 0.8 μg/dl for the period 1400–1600 ($P < 0.05$)], whereas they increased significantly in the postnap period compared with those that did not nap (1.1 ± 0.5 μg/dl for the period 1600–2230, $P < 0.05$; Fig. 2). No gender effects were observed.

IL-6. Daytime napping following a night of total sleep deprivation affected both nap and postnap IL-6 plasma levels. IL-6 significantly decreased during the nap and tended to remain lower in the postnap period compared with the no-nap group [between-group difference, nap vs. no-nap of the change in IL-6 levels before and after sleep loss was -1.7 ± 0.7 pg/ml for the nap period ($P < 0.05$) and -0.9 ± 0.6 pg/ml for the postnap period ($P = 0.1$), respectively; Fig. 3]. No gender effects were observed.

TNF-α and TNFR1. No effects of daytime napping on TNF-α or TNFR1 levels were detected during the nap and postnap periods.
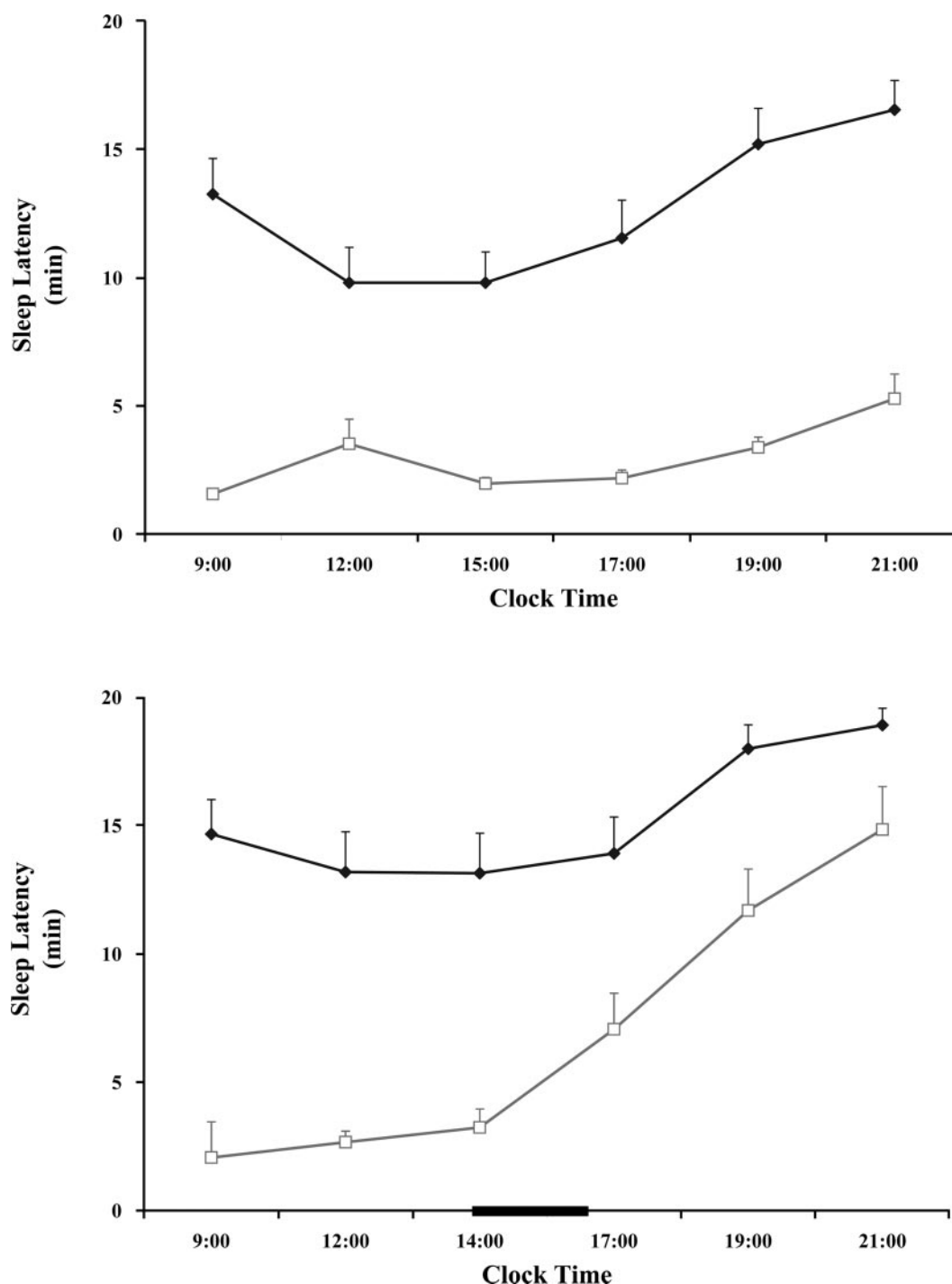
Fig. 1. Multiple sleep latency test mean values pre- (◆) and post- (□) sleep deprivation in the no-nap group (*top*) and the nap group (*bottom*). Thick black line in the abscissa indicates nap sleep recording period. Significant reduction of sleepiness in the postnap period (1600–2100), $P < 0.05$.

DISCUSSION

This study is the first to evaluate in an integrated and systematic way the effects of daytime napping on sleepiness, performance, and hormones/cytokines that appear to mediate arousal and sleepiness in humans. The results of the study suggest that a 2-h midafternoon nap after a night of sleep loss restores, to a significant degree, alertness and tends to improve, to a lesser degree, performance. In addition, these behavioral changes appear to be associated with parallel increases in

cortisol levels and decreases in IL-6 levels, with both of these changes promoting alertness and better performance.

Several studies have reported an increase in neurobehavioral performance following naps of durations ranging between 15 min and 2 h during total sleep deprivation of between 36 and 88 h (24). The effects of naps on alertness are less clear, with some authors reporting little or no subjective alerting effects of naps and others reporting elevated objective alertness levels following naps (11, 24). In our study, there was a strong and
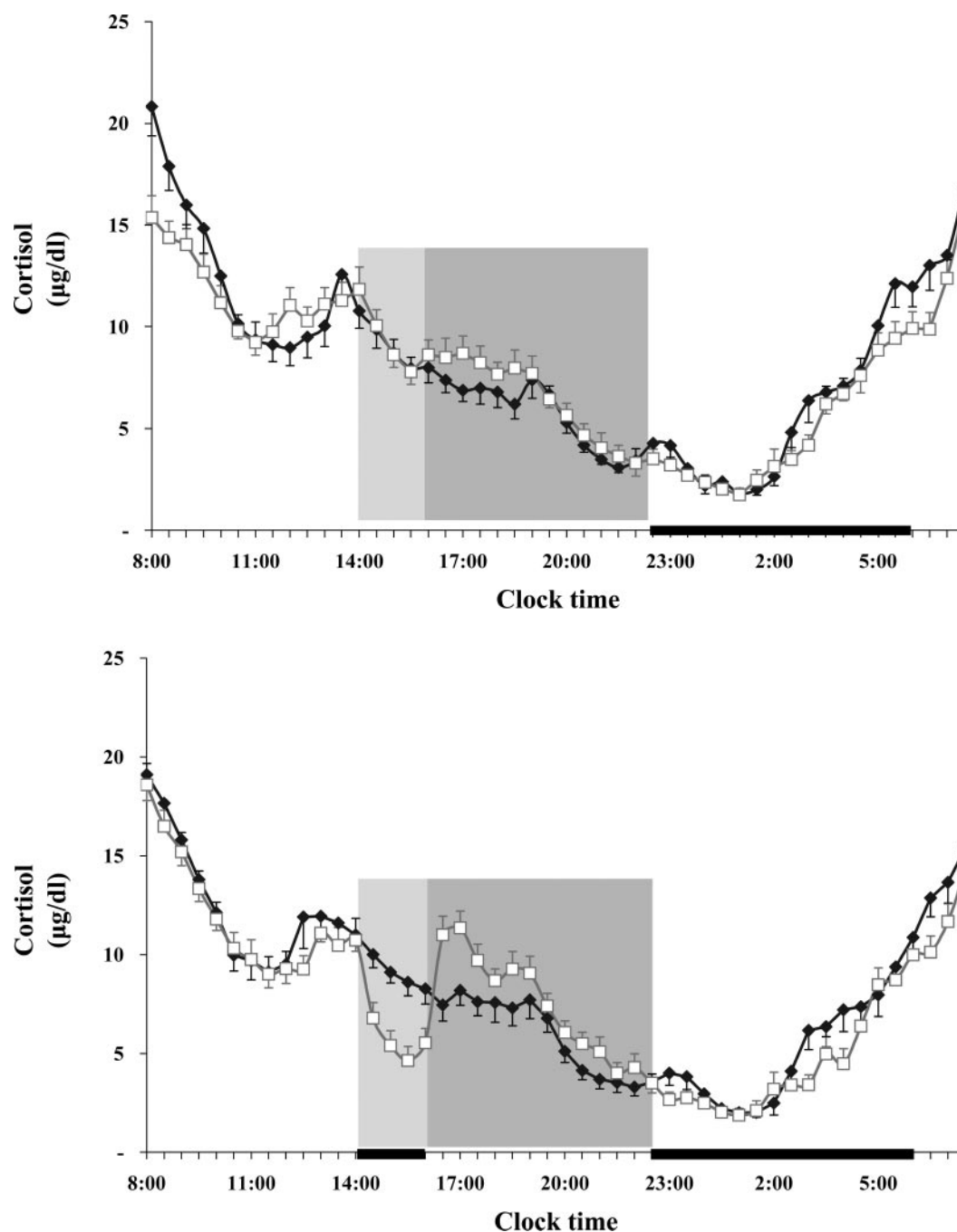
Fig. 2. Twenty-four-hour cortisol values pre- (◆) and post- (□) sleep deprivation in the no-nap group (*top*) and the nap group (*bottom*). Thick black lines in the abscissa indicate nighttime and nap sleep recording periods. Significant reduction and increase of cortisol during the nap (1400–1600) and the postnap period (1600–2200), respectively, $P < 0.05$.

significant improvement in objective sleepiness associated with improvement of subjective sleepiness that became significant about 4 h after the end of the nap. The delayed and relatively weak improvement in subjective sleepiness, compared with objective sleepiness, may indicate either prolonged significant subjective effects of sleep inertia or that the restoration of alertness has not reached a threshold necessary to be experienced as feeling refreshed and energetic. Furthermore, in our study, the strongest effect appeared to be on objective sleepiness, i.e., MSLT, whereas

neurobehavioral performance (PVT) was improved to a lesser degree. The dissociation of the response between the two objective tests may indicate that they may be measuring different central nervous system functions, although they correlate strongly, as indicated by their similar response after significant total or partial sleep loss (29, 31). Alternative explanations for the marginal improvement in PVT performance is that recovery is rather delayed and/or that longer duration of PVT session, i.e., 30 vs. 10 min, might be more sensitive in detecting decrements/improvement (1, 2).
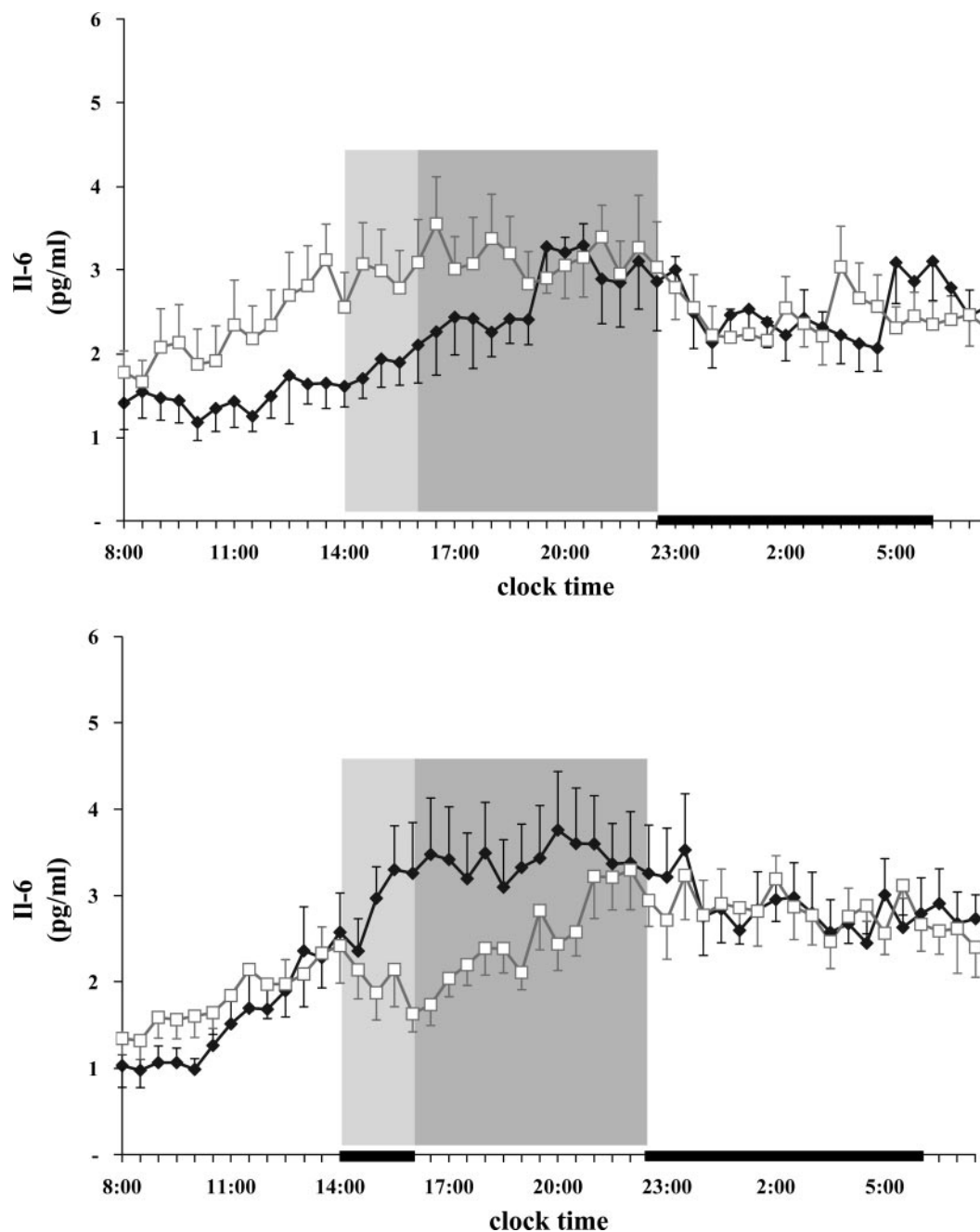
Fig. 3. Twenty-four-hour IL-6 values pre- (◆) and post- (□) sleep deprivation in the no-nap group (*top*) and the nap group (*bottom*). Thick black lines in the abscissa indicate nighttime and nap sleep recording periods. Significant reduction of IL-6 during the nap period (1400–1600), $P < 0.05$.

It should be noted that, although a 2-h midafternoon nap restored alertness to a significant degree, alertness did not reach baseline presleep deprivation levels, suggesting that a 2-h deep sleep is not adequate for a complete restoration of alertness and vigor following sleep loss.

Our findings that IL-6 is increased after a night of total sleep loss and that its plasma levels dropped after a 2-h nap support the view that IL-6 plays a role in sleep homeostasis in humans. In earlier studies, daytime levels of IL-6 increased after total or partial sleep loss (25, 31, 34) and tended to decrease during the recovery night. The sharp drop of IL-6 in the middle of the day following a 2-h nap is consistent with a reduction of the

postdeprivation increased sleep drive and fits with the humoral homeostatic model of sleep in humans (4, 14). In this model, SWS, and particularly Stage 4, is a correlate of a metabolic process that reverses some of the effects of waking on the brain (8). The proposed role of IL-6 in sleep homeostasis is consistent with earlier studies that showed that average daily IL-6 levels were higher in total sleep deprivation compared with partial sleep deprivation (25).

The proinflammatory cytokines IL-6 and TNF-α have been suggested as mediators of excessive sleepiness in humans in pathological conditions, e.g., sleep apnea (33, 36) and narcolepsy (18), or in experimentally induced sleepiness, i.e., fol-

lowing sleep deprivation (25, 31, 34). In our study, the parallel decrease of objective sleepiness and IL-6 levels during the postnap period support that IL-6 is a sleepiness-mediating cytokine. However, neither TNF-α nor TNFR1 were increased following a night of sleep loss, and their levels were not affected by the 2-h nap. Previous studies have shown a slight increase of TNF-α in men after 1 wk of partial sleep loss (31) and an increase of TNFR1, but not TNF-α, in an experiment of 88 h of total sleep loss (25). Whether these results indicate that prolonged sleep deprivation is necessary before the effect on TNF is evident or that TNF has only a limited role in sleep homeostasis in humans remains to be determined. It is interesting to note that the findings that TNF-α levels are elevated in conditions of pathological sleepiness, e.g., sleep apnea, obesity, and narcolepsy, are consistent and confirmed in several studies (18, 33, 36).

With regard to the effects of napping on cortisol, there were two interesting findings. The first was the marked and significant drop of cortisol levels during napping. The 24-h cortisol profile is not markedly affected by the absence of sleep or by sleep at an unusual time of day (28). It appears that sleep onset is associated with a short-term inhibition of cortisol secretion, whereas the end of sleep is followed by an increase of cortisol secretion. Several studies have examined the effect of daytime sleep of 4–8 h duration on cortisol after a night of sleep deprivation, with some of them reporting a significant but modest effect (27, 40) and others no effect (19, 39). One possible explanation for the negative studies is that sleep was initiated in the morning at the time of the daily maximum of HPA axis activity (28). In our study, by design, daytime sleep (nap) was of short duration and at a time of the day most people usually nap, thus mimicking "real-life" situations. We believe that the strong and marked effect of 2-h midafternoon napping on cortisol is related to the timing of the nap that coincides with a secondary peak of sleepiness in humans (15) and that one-half of the nap consisted of SWS, which appears to be the stage most strongly associated with the cortisol decrease during sleep (28, 35). The second finding was the significant transient increase of cortisol during the postnap period. This significant increase paralleled the significant improvement of objective and subjective sleepiness and suggests that relatively lower levels of cortisol are associated with sleep/sleepiness, whereas relatively higher levels of cortisol are associated with wake/alertness, respectively. The increase of cortisol after subjects were awakened from their naps is probably an adaptive response to the stress of waking (6) and is not related to the upright position (12) or the transition from dim light to bright light (16), since the subjects remained in a lying or sitting position when awakened, and the light in the sleep room was much less bright (31) compared with that of previous reports.

We (30, 32) have previously suggested that the interaction of cortisol and IL-6 peripheral levels determines the levels of sleepiness and fatigue. Specifically, the combination of relatively high IL-6 levels and relatively low cortisol levels is associated with sleep/sleepiness, whereas the combination of relatively high IL-6 levels and relatively high cortisol levels is associated with poor sleep and fatigue (lack of objective sleepiness). The nap effects on IL-6 and cortisol support such a model, as postnap increased alertness was associated with relatively higher cortisol and relatively lower IL-6 levels during the corresponding period.

In terms of sleep physiology, the increase in the amount of Stage 4 sleep was notably similar between the 10-h and the 8-h recovery sleep in the nap and no-nap conditions, respectively, and all of the Stage 4 sleep lost during sleep deprivation was recovered. In contrast, the increase in SWS sleep, primarily accounted for by the increase of Stage 3 sleep, was significantly higher in the 10-h recovery sleep, suggesting that after sleep loss extended sleep is associated with a stronger build-up of Stage 3 sleep. Whether these differences between the build-up of Stage 4 and Stage 3 sleep following sleep loss reflect differences in terms of underlying metabolic processes between the two stages is unknown. Δ power was equally increased in the nap and no-nap conditions and to a degree similar to previous deprivation studies in humans (5). However, in the nap condition, most of the recovery of Δ power occurred during the nap, whereas in the subsequent night there was decrease of Δ power compared with baseline. The large increase of Δ power during the nap is consistent with the strong effect of napping on cortisol and IL-6 levels. Furthermore, in our study, REM sleep was increased in the nap condition but not in the no-nap condition. This suggests that the nap, by recovering most of the lost Δ power, allows REM sleep to occur in the subsequent night. Our findings on REM recovery are similar to earlier reports (4, 8) that after sleep loss SWS is the first sleep stage to be restored, followed by REM sleep, suggesting a stronger biological drive to restore SWS sleep compared with REM sleep. Finally, intermittent wakefulness was not decreased in the postdeprivation night, most likely due to the disturbing effects of the intravenous catheter.

In this study, no gender effects were detected in terms of behavioral or hormonal responses to the 2-h nap. This appears to be different from our earlier finding of differential-gender sleep and hormonal responses after 1 wk of partial sleep restriction (31). In contrast to the nap study, in the partial sleep restriction experiment, young women had a significantly higher amount of SWS than men, which may explain the gender effects observed in this study. Notably, women in general, including young women, have a higher amount of SWS than men (3, 21, 38), and in this regard, the women in our nap study may not be representative of the majority of young, healthy women. Thus the possibility of gender effects remains open and should continue to be one of the objectives of future sleep research.

In summary, a 2-h midafternoon nap improves alertness and, to a lesser degree, performance and reverses the effects of one night of sleep loss on cortisol and IL-6 secretion. The redistribution of cortisol secretion and the prolonged suppression of IL-6 secretion are beneficial, as they improve alertness and performance. Improved alertness and performance were associated with increased cortisol and decreased IL-6 levels, suggesting their roles as arousal and sleepiness factors, respectively, in humans.

REFERENCES

1. **Anderson C, Horne JA.** Sleepiness enhances distraction during a monotonous task. *Sleep* 29: 573–576, 2006.

2. **Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ.** Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *J Sleep Res* 12: 1–12, 2003.

3. **Bixler EO, Vgontzas AN, Lin HM, Vela-Bueno A, Kales A.** Normal sleep and sleep stage patterns: effects of age, BMI and gender. *Sleep* 26 *Suppl:* A61–A62, 2003.

4. **Borbély AA.** A two-process model of sleep. *Hum Neurobiol* 1: 195–204, 1982.

5. **Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D.** Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol* 51: 483–495, 1981.

6. **Born J, Hansen K, Marshall L, Mölle M, Fehm HL.** Timing the end of nocturnal sleep. *Nature* 397: 29–30, 1999.

7. **Dinges DF, Whitehouse WG, Carota Orne E, Ome MT.** The benefits of a nap during prolonged work and wakefulness. *Work Stress* 2: 139–153, 1988.

8. **Feinberg I, March JD, Floyd TC, Jimison R, Bossom-Demitrack L, Katz PH.** Homeostatic changes during post-nap sleep maintain baseline levels of delta EEG. *Electroencephalgr Clin Neurophysiol* 61: 134–137, 1985.

9. **Follenius M, Brandenberger G, Bandesapt JJ, Libert JP, Ehrhart J.** Nocturnal cortisol release in relation to sleep structure. *Sleep* 15: 21–27, 1992.

10. **Harris TM, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH Jr, Heimovitz H, Cohen HJ, Wallace R.** Associations of elevated interleukin-6 and c-reactive protein levels with mortality in the elderly. *Am J Med* 106: 506–512, 1999.

11. **Helmus T, Rosenthal L, Bishop C, Roehrs T, Syron ML, Roth T.** The alerting effects of short and long naps in narcoleptic, sleep deprived, and alert individuals. *Sleep* 20: 251–257, 1997.

12. **Hennig J, Friebe J, Ryl I, Kramer B, Bottcher J, Netter P.** Upright posture influences salivary cortisol. *Psychoneuroendocrinology* 25: 69–83, 2000.

13. **Hoddes E, Zarcone V, Smythe HR, Dement WC.** Quantification of sleepiness: a new approach. *Psychophysiology* 10: 431–436, 1973.

14. **Krueger JM, Obal FJ, Fang J, Kubota T, Taishi P.** The role of cytokines in physiological sleep regulation. *Ann NY Acad Sci* 933: 211–221, 2001.

15. **Lavie P.** Ultrashort sleep-waking schedule. III. "Gates" and "forbidden zones" for sleep. *Electroencephalogr Clin Neurophysiol* 63: 414–425, 1986.

16. **Leproult R, Colecchia EF, L'Hermite-Baleriaux M, Van Cauter E.** Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels. *J Clin Endocrinol Metab* 86: 151–157, 2001.

17. **Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, Loriaux DL, Chrousos GP.** Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. *N Engl J Med* 316: 1309–1315, 1987.

18. **Okun ML, Glese S, Lin L, Einen M, Mignot E, and Coussons-Read ME.** Exploring the cytokine and endocrine involvement in narcolepsy. *Brain Behav Immun* 18: 326–332, 2004.

19. **Pietrowsky R, Meyrer R, Kern W, Born J, Fehm HL.** Effects of diurnal sleep on secretion of cortisol, luteinizing hormone, and growth hormone in man. *J Clin Endocrinol Metab* 78: 683–687, 1994.

20. **Rechtschaffen A, Kales A.** *Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Los Angeles: UCLA Brain Information Services, 1968.

21. **Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A.** The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med* 164: 406–418, 2004.

22. **Richardson GS, Carskadon MA, Flagg W, van den Hoed J, Dement WC, Mitler MM.** Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalgr Clin Neurophysiol* 45: 621–627, 1978.

23. **Ridker PM, Rifai N, Stampfer MJ, Hennekens CH.** Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 101: 1767–1772, 2000.

24. **Rogers NL, Dorrian J, Dinges DF.** Sleep, waking and neurobehavioural performance. *Front Biosci* 8: s1056–s1067, 2003.

25. **Shearer WT, Reuben JM, Mullington JM, Price NJ, Lee BN, Smith EO, Szuba MP, Van Dongen HP, Dinges DF.** TNF-α receptor 1 and IL-6 plasma levels in humans subjected the sleep deprivation model of spaceflight. *J Allergy Clin Immunol* 107: 165–170, 2001.

26. **Takahashi M.** The role of prescribed napping in sleep medicine. *Sleep Med Rev* 7: 201–202.

27. **Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S, Polonsky KS.** Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *J Clin Invest* 88: 934–942, 1991.

28. **Van Cauter E.** Endocrine physiology. In: *Principles and Practices of Sleep Medicine* (4th ed.). Philadelphia, PA: Elsevier-Saunders, 2005, sect. 3, pt. I, chapt. 22, p. 266–282.

29. **Van Dongen HP, Maislin G, Mullington JM, Dinges DF.** The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2: 117–126, 2003.

30. **Vgontzas AN, Bixler EO, Lin HM, Prolo P, Trakada G, Chrousos GP.** IL-6 and its circadian secretion in humans. *Neuroimmunomodulation* 12: 131–140, 2005.

31. **Vgontzas AN, Zoumakis E, Bixler EO, Lin HM, Follett H, Kales A, Chrousos GP.** Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* 89: 2119–2126, 2004.

32. **Vgontzas AN, Zoumakis M, Papanicolaou DA, Bixler EO, Prolo P, Lin HM, Vela-Bueno A, Kales A, Chrousos GP.** Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism* 7: 887–892, 2002.

33. **Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP.** Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 85: 1151–1158, 2000.

34. **Vgontzas AN, Papanicolaou DA, Bixler EO, Lotsikas A, Zachman K, Kales A, Prolo P, Wong ML, Licinio J, Gold PW, Hermida RC, Mastorakos G, Chrousos GP.** Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab* 84: 2603–2607, 1999.

35. **Vgontzas AN, Mastorakos G, Bixler EO, Kales A, Gold PW, Chrousos GP.** Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. *Clin Endocrinol (Oxf)* 51: 205–215, 1999.

36. **Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP.** Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 82: 1313–1316, 1997.

37. **Vgontzas AN, Chrousos P.** Sleep, the hypothalamic-pituitary-adrenal axis and cytokines: multiple interactions and disturbances in sleep disorders. *Endocrinol Metab Clin N Am* 31: 15–36, 2002.

38. **Walsleben JA, Kapur VK, Newman AB, Shahar E, Bootzin RR, Rosenberg CE, O'Connor G, Nieto FJ.** Sleep and reported daytime sleepiness in normal subjects: the Sleep Heart Health Study. *Sleep* 27: 293–298, 2004.

39. **Weibel L, Follenius M, Spiegel K, Ehrhard J, Brandenberger G.** Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. *Sleep* 18: 549–556, 1995.

40. **Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J.** Cortisol secretion is inhibited during sleep in normal man. *J Clin Endocrinol Metab* 56: 352, 1983.