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

A. N. Vgontzas, S. Pejovic, E. Zoumakis, H. M. Lin, E. O. Bixler, M. Basta, J. Fang, A. Sarriogianidis, and G. P. Chrousos. 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 total sleep loss). 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 were completed on the fourth (predeprivation) and sixth days (postdeprivation). After the nap they experienced significantly less sleepiness in humans and have been shown to be associated with increased arousal-promoting hormones, i.e., cortisol, and a decrease of sleepiness-mediating inflammatory cytokines, such as IL-6 and TNF-α. We conclude that a 2-h midafternoon nap improves alertness, and to a lesser degree performance, 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 paraventricular 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 (pre-deprivation) 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 perfusion 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 0800, 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

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Sleep</td>
<td>Loss</td>
<td>Recovery</td>
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<td>Sleep lab</td>
<td>1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Nighttime</td>
<td>2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MSLT</td>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Subjective sleepiness</td>
<td>4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>PVT</td>
<td>5</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>2-h nap* (1400–1600)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood drawing</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*50% of the subjects completed the 2-h nap. MSLT, multiple sleep latency test; PVT, psychomotor vigilance test.
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 post-deprivation) 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 (pre-deprivation) 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 (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 I/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 \( \Delta \) and a 4.0- to 7.0-Hz band for \( \Theta \) was used. The results of the FFT were averaged during non-REM sleep for further statistical analyses.

Data are presented as means ± 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 ± 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 ± 1.1% SWS; 1.19 ± 0.4% Stage 1; 6.41 ± 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
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 $\Delta$ and $\Theta$ power during non-REM sleep on postdeprivation night compared with baseline ($31.0 \pm 8.6\%$ increase for $\Delta$ power and $26.2 \pm 6.3\%$ increase for $\Theta$ power, both $P < 0.01$).

Similarly, in the nap group, subjects demonstrated a significant increase in the total amount of $\Delta$ 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 $\Theta$ power on the postdeprivation nap plus night compared with baseline ($37.1 \pm 6.6\%, P < 0.01$). The largest increases of $\Delta$ and $\Theta$ power per epoch were observed during the nap sleep ($60.0 \pm 11.7$ 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 $\Delta$ 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: $-10.05 \pm 0.3$ min in the no-nap group, $-9.55 \pm 0.3$ 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 $0.51 \pm 0.4$ 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; $-11.8 \pm 0.9$ min in the no-nap group; $-4.6 \pm 0.9$ min in the nap group; difference of the differences of the mean MSLT values in the postnap period between the two groups was $7.3 \pm 1.6$ 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: $-1.1 \pm 0.7$, $P = 0.1$ for the visual-analog scale, and $0.7 \pm 0.4$, $P < 0.1$ for the Stanford sleepiness scale). This trend reached significance for the Stanford Sleepiness Scale in the late postnap period (2000–2200; difference of $0.9 \pm 0.4$, $P < 0.05$).

**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 $1.2$ ($P < 0.06$).

### 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

<table>
<thead>
<tr>
<th>Recovery Sleep - Baseline Sleep</th>
<th>No-Nap Condition (n = 21)</th>
<th>Nap Condition* (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3, min</td>
<td>12.0±4.0</td>
<td>22.0±4.1</td>
</tr>
<tr>
<td>Stage 4, min</td>
<td>25.5±5.7</td>
<td>29.5±5.9</td>
</tr>
<tr>
<td>SWS, min</td>
<td>37.7±4.8</td>
<td>51.3±4.9*</td>
</tr>
<tr>
<td>REM, min</td>
<td>0.5±5.7</td>
<td>28.5±5.8*</td>
</tr>
</tbody>
</table>

Data represent means ± 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). $*P < 0.05$; $\dagger P = 0.056$.

**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 $-3.3 \pm 0.8$ $\mu$g/dl for the period 1400–1600 ($P < 0.05$)], whereas they increased significantly in the postnap period compared with those that did not nap ($1.1 \pm 0.5$ $\mu$g/dl for the period 1600–2300, $P < 0.05$; 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 $-1.7 \pm 0.7$ pg/ml for the nap period ($P < 0.05$) and $-0.9 \pm 0.6$ 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.

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

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

Data represent means ± SE.
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
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).
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-

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**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.
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 inter-
esting 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 sev-
eral studies (18, 33, 36).

With regard to the effects of napping on cortisol, there were
two interesting findings. The first was the marked and signif-
ificant 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 re-
sponse 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 rela-
tively 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 dur-
ing 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 signifi-
cantly 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. ∆ power was equally
increased in the nap and no-nap conditions and to a degree
similar to previous deprivation studies in humans (5). How-
ever, in the nap condition, most of the recovery of ∆ power
occurred during the nap, whereas in the subsequent night there
was decrease of ∆ power compared with baseline. The large
increase of ∆ 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 ∆ 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 redis-
tribution of cortisol secretion and the prolonged suppression
of IL-6 secretion are beneficial, as they improve alertness and
performance. Improved alertness and performance were asso-
ciated with increased cortisol and decreased IL-6 levels, sug-
gesting their roles as arousal and sleepiness factors, respec-
tively, in humans.

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