The Impact of Moderate Sleep Loss on Neurophysiologic Signals during Working-Memory Task Performance

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Study Objectives: This study examined how sleep loss affects neurophysiologic signals related to attention and working memory.

Design: Subjective sleepiness, resting-state electroencephalogram, and behavior and electroencephalogram during performance of working-memory tasks were recorded in a within-subject, repeated-measures design.

Setting: Data collection occurred in a computerized laboratory setting.

Participants: Sixteen healthy adults (mean age, 26 years; 8 female)

Interventions: Data from alert daytime baseline tests were compared with data from tests during a late-night, extended-wakefulness session that spanned up to 21 hours of sleep deprivation.

Measurements and Results: Alertness measured both subjectively and electrophysiologically decreased monotonically with increasing sleep deprivation. A lack of alertness-related changes in electroencephalographic measures of the overall mental effort exerted during task execution indicated that participants attempted to maintain high levels of performance throughout the late-night tests. Despite such continued effort, responses became slower, more variable, and more error prone within 1 hour after participants' normal time of sleep onset. This behavior failure was accompanied by significant degradation of event-related brain potentials related to the transient focusing of attention.

Conclusions: Moderate sleep loss compromises the function of neural circuits critical to subsecond attention allocation during working-memory tasks, even when an effort is made to maintain wakefulness and performance. Multivariate analyses indicate that combinations of working-memory-related behavior and neurophysiologic measures can be sensitive enough to permit reliable detection of such effects of sleep loss in individuals. Similar methods might prove useful for assessment of functional alertness in patients with sleep disorders.

Key Words: Fatigue, alertness, cognition, attention, working memory, electroencephalogram, event-related potentials

INTRODUCTION

This paper examines the impact of moderate sleep loss on behavior and neurophysiologic measures related to working-memory task performance. In children and adolescents, sleep loss tends to be associated with impaired performance on neuropsychologic tests and lower levels of scholastic achievement.1-3 Equivalent patterns of degraded performance on the job or on controlled tests have been observed in working adults experiencing interruption of normal sleep patterns.4-7 Not surprisingly then, sleep loss is frequently implicated in major workplace accidents.8,9 Many such accidents likely result from the fact that, although rote activities might be performed adequately even after moderate sleep loss, subtle changes in a drowsy individual's cognitive ability might nonetheless diminish his or her capacity to respond optimally when circumstances arise that require rapid evaluation and thoughtful action.

The ability to perform competently in such attention-demanding circumstances depends in part on the integrity of working memory. Working memory refers to the limited capacity to hold and manipulate information in mind for several seconds in the context of cognitive activity. In a sense, working memory is an outcome of the ability to control and sustain attention and to strategically focus it on a particular mental representation in the face of distracting influences.10,11 This ability plays an important role in comprehension, reasoning, planning, and learning.12 Indeed, the use of active mental representations to guide performance appears critical to behavior flexibility.13,14 and measures of this ability tend to be positively correlated with performance on psychometric tests of cognitive ability and other indexes of scholastic aptitude.15-17

Metabolic studies suggest that working memory and the neural mechanisms of attention control involve cortical circuits linking regions of prefrontal cortex with posterior association cortices.18-22 Activation of these circuits also occurs during reasoning and problem solving.23-25 Such activation can be detected in measurements of neuroelectric activity recorded at the scalp. More specifically, a sustained-task-imposed change in working-memory requirements tends to produce characteristic tonic changes in the amplitude of attention-related spectral features of the ongoing electroencephalogram (EEG)26-28 that are punctuated by more phasic changes in components of the stimulus-locked, transient event-related potentials (ERP).29,31

Under normal conditions, neurophysiologic signals modulated by task-imposed variations in working-memory demands tend to be very stable. For example, in a recent study in which the test-retest reliability of task-related EEG spectral features was examined in well-practiced subjects, correlations of r > .9 were found between two test sessions with a 1-week lag.32 Despite this apparent stability when other factors are held constant, there is evidence that task-related neurophysiologic signals are highly sensitive to stressors that impose some form of mild, transient cognitive impairment. For example, recent studies have demonstrated that working-memory-sensitive neurophysiologic signals vary in conjunction with low doses of alcohol33-35; diphenhydramine36; marijuana36; and prescription medications frequently used to treat neurologic37 and psychiatric38 disorders.

Results of this type suggest that the cortical networks responsible for generating working-memory-sensitive neurophysiologic signals might also be disrupted in conjunction with moderate sleep loss. To evaluate this possibility, the current study examined the impact of extended

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wakefulness on behavior and neurophysiologic measures made during performance of well-practiced working-memory tasks. Data from a sample of healthy young adult subjects were compared between an average alert daytime baseline test interval and 5 nighttime test intervals that occurred over the course of an extended-wakefulness session in which the participants performed tasks throughout a night of sleep deprivation.

METHODS

Subjects

Sixteen healthy adults (21-32 years; mean age, 26 years; 8 females) participated. Most were full-time college students and as such they tended to maintain fairly irregular sleep-wake schedules. All were non-smokers, social drinkers (1-10 drinks per week), and mild to moderate caffeine consumers (1-3 cups of coffee per day). None were taking any centrally acting medications during the course of the study, and none had been previously diagnosed with any psychiatric or neurologic problems or sleep disorders. All participation was fully informed and voluntary and conformed to all institution and government guidelines for the protection of human subjects. Participants were remunerated on an hourly basis for their efforts. To minimize attrition, a significant bonus was also awarded to all participants upon completion of all test sessions. Finally, to increase motivation to task performance, extra bonus payments were awarded in a competitive fashion to the two participants who had the best overall accuracy across all test sessions.

Tasks

The focus of the present paper is on the effects of sleep deprivation during working-memory tasks. Participants performed two difficulty levels of a continuous performance, n-back–style working-memory-task versions of which we have employed in prior EEG studies. Similar n-back tasks have been adopted in many other laboratories as a means to activate functional networks of working memory in a controlled fashion. Such applications have spanned conventional behavior studies, other electrophysiologic studies, studies of the effects of magnetic fields on cognitive function, and functional neuroimaging studies employing positron emission tomography or functional magnetic imaging methods.

In the versions of this task employed in the present study (Figure 1), participants were required to compare the spatial location of the current stimulus with that of one presented previously. Briefly, single capital-letter stimuli, drawn randomly from a set of 12, were presented for 200 milliseconds. The letter stimulus occurred 1.3 seconds after the cue in one of 12 possible locations on the screen. Prior to stimulus onset, a warning cue (a small x) appeared in the center of the screen for 200 milliseconds. The letter stimulus occurred 1.3 seconds after the cue and its spatial position varied randomly from trial to trial. A small fixation dot was continuously present at the center of the screen.

In an easy, low-working-memory-load version of the task, subjects were required to match the position of the current stimulus with the position of the very first stimulus in the block. In a difficult, high-working-memory-load version of the task, participants compared the current stimulus with that presented two trials previously. In this version, they were required to remember two positions (and their sequential order) for the duration of 2 trials (9 seconds) and to update that information on each subsequent trial. In both versions of the task, stimuli were presented in blocks of 53 trials (the first 3 trials were warm-up trials and were discarded from analysis). Matches occurred randomly on 50% of the trials. Participants were instructed to respond as quickly and as accurately as possible.

Procedures

Each subject participated in a total of 6 experimental sessions. The first session was a practice session in which subjects learned to perform the working-memory tasks to an asymptotic level. All subjects then participated in 5 subsequent sessions, separated by at least 1 week. Four sessions involved recording from participants before and after they had ingested alcohol, caffeine, antihistamine, or placebo. These sessions occurred in a counter-balanced order, and the data concerning drug effects are described in a separate report. A fifth experimental session was an extended-wakefulness manipulation that began in the evening and lasted until 6:00 AM the following morning. This extended-wakefulness session is the focus of the current report. However, since each of the four drug sessions involved a baseline recording prior to drug administration (around 12:00 PM on each day), the average of these alert, daytime, baseline sessions was used as a comparison point for the data collected in the extended-wakefulness session. In the week prior to the extended-wakefulness session, participants were required to keep a sleep diary indicating (among other things) the time on each day they went to sleep and the time they awoke.

In the overnight extended-wakefulness session, subjects arrived at the laboratory at approximately 8:30 PM, were given a warm-up block of the working-memory task and other tasks, and were prepared for the EEG recording. They then participated in five 40-minute recording intervals spaced throughout the night. The first interval occurred on average at 11:00 PM, the second at 12:30 AM, the third at 1:30 AM, the fourth at 3:30 AM, and the fifth at 5:00 AM. The internal structure of each interval was the same as that used during the daytime baseline sessions. Within each interval, participants completed the Karolinska* Subjective Sleepiness Rating Scale and had their EEG recorded while they performed two blocks each of the easy and difficult versions of the working-memory task. At each interval, EEG data were also recorded while the participants rested quietly for 90 seconds with their eyes open and closed. Such resting-state data were analyzed in order to obtain objective neurophysiologic measures of changes in alertness.

The resting conditions, the subjective measures, and the four blocks of the working-memory task took approximately 20 minutes to complete during each testing interval. In the periods between these recording blocks, the participants performed other repetitive computer tasks to ensure continued wakefulness and to help induce mental fatigue. Thus, at each of the test intervals, participants also performed a 10-minute version of the Psychomotor Vigilance Task, which is a simple reaction-time task that has been frequently used in sleep deprivation studies, and a 5-minute version of the Multi-Attribute Task Battery, which is a computer-based multitasking environment that simulates some of the activities a pilot might be required to perform and that has often been
employed in studies of mental workload. At three occasions over the extended-wakefulness testing session, participants also performed a 20-minute version of a simple visual “oddball” discriminative judgment vigilance task. During periods when the participants were not actively involved in one of the formal tasks, they were allowed to read, play video games, or surf the Internet, but no napping was permitted.

**EEG Recording and Preprocessing**

The EEG was continuously recorded from 28 scalp electrodes using a linked-mastoids reference. The electrooculogram was recorded from electrodes placed above and below one eye and at the outer canthus of each eye. Physiologic signals were band-pass filtered at 0.01 hertz to 100 hertz and sampled at 256 hertz. Data were digitally filtered offline with a zero-phase-shift, 0.5 hertz, high-pass IIR filter. Automated artifact detection was followed by application of adaptive eye-contaminant removal filters. The data were then visually inspected, and data segments containing possible residual artifacts were eliminated from subsequent analyses. To obtain power spectral estimates, Fast Fourier transforms were applied, and periodograms were computed on 50% overlapping, 512-sample Hanning windows for all artifact-free trials and averaged over all data within a condition. Average spectra were converted to dB power by normalizing them with a log10 transform. The ERP were computed by averaging together all of the artifact-free epochs of the stimulus-locked EEG for correctly classified trials within each condition for each subject. These epochs began 0.2 seconds before stimulus onset and extended to 1.0 second afterward. The ERP were low-pass filtered at 20 hertz prior to subsequent analyses.

**Analyses**

To examine how individual behavior and physiologic features varied over the extended test session, univariate repeated measures analyses of variance were used to compare data from the 12:00 PM baseline to data recorded across the different test intervals of the extended-wakefulness session. The experiment-related sources of variance in each of the individually measured parameters were assessed in univariate task (easy vs. difficult) or resting condition (eyes-open vs. eyes-closed) by test interval repeated measures ANOVA. Changes in mental function related to extended wakefulness would thus be expected to manifest as a main effect of test interval or as an interaction involving test interval. The Greenhouse-Geisser correction to degrees-of-freedom was employed to correct for any violations of the sphericity assumption in analyses involving repeated measures. In such cases, the reported p values correspond to the corrected degrees of freedom.

**RESULTS**

The sleep-diary data indicated that over the week prior to the extended-wakefulness session, the participants typically fell asleep between 11:30 PM and 1:00 AM and received about 7 hours (range, 6-9 hours) of sleep on an average night. On the day of the extended-wakefulness session, participants reported awakening between 6:00 AM and 10:30 AM (average, 8:00 AM) after having obtained an average of 7 hours of sleep. Thus, the first test (11:00 PM) during the extended-wakefulness session occurred, on average, after 15 hours of wakefulness, and the final test session at 5:00 AM took place after about 21 hours (range, 19.5 to 23 hours) of wakefulness.

No caffeinated beverages were consumed during the extended-wakefulness session itself. Twelve of the participants consumed no caffeine after noon of the day of the extended-wakefulness session. The other 4 participants had last consumed caffeinated beverages in the late afternoon. None consumed a total of more than three caffeinated beverages on the day of the extended-wakefulness session.

**Impact of Extended Wakefulness on Subjective and EEG Measures of Sleepiness**

Subjectively, participants reported that they felt most alert in the 12:00 PM baseline interval and progressively less alert at later test intervals, with minimal alertness usually reached during the final test at about 5:00 AM (Figure 2). This change was reflected in a significant main effect of test interval (F(5,75) = 23.31; P < .001). Posthoc pair-wise comparisons indicated that although there was no significant difference between the 11:00 PM interval and the 12:00 PM baseline, subjects had become significantly sleepy (P < .01) by the 12:30 AM interval.

Eye-movement activity and EEG spectra recorded while the participants rested quietly displayed classic signs of sleepiness, providing convergent evidence that alertness decreased approximately linearly over the course of the extended-wakefulness session. For example, past research has indicated that horizontal slow eye movements tend to increase as individuals become increasingly sleepy. To measure

![Figure 2](image-url)  
**Figure 2**—Average (±SEM) subjective sleepiness ratings assessed with the Karolinska Sleepiness Scale. Sleepiness did not differ significantly between the 12:00 PM alert baseline and the 11:00 PM test interval. It increased in an approximately linear fashion from the 11:00 PM test interval to the 5:00 AM test interval.

![Figure 3](image-url)  
**Figure 3**—Average electroencephalographic power recorded from a midline occipital electrode in the resting eyes-closed (top) and eyes-open (bottom) conditions during the 12:00 PM baseline and during the 5 AM test interval. In both conditions, electroencephalographic power below the alpha band was relatively higher at the 5 AM test interval. In contrast, alpha-band power was relatively attenuated at 5 AM in the eyes-closed condition.
changes in the incidence of slow eye movements, a bipolar derivation was computed between a pair of electrodes placed at the outer canthi of the eyes, and average power in a 0.5-hertz to 1.0-hertz band was extracted from this derivation prior to removal of eye-movement contaminants. By this measure, slow eye movements increased significantly over the test session \((F(5,75) = 10.52; P < .001)\).

Past studies have also consistently demonstrated a drowsiness-related pattern of changes in the spectral composition of the resting state EEG\(^ {57-61}\). In general, particularly during eyes-closed resting conditions over parietooccipital electrode locations, spectral power in the delta and theta bands tends to increase during sleepy states, whereas alpha-band power tends to decrease. These effects were observed in the present data (Figure 3). Specifically, across resting conditions, delta activity measured as the average power between 2 hertz and 4 hertz at electrode Pz increased over test intervals \((F(5,75) = 3.87, P = .01)\), as did posterior theta measured as the average power between 4 hertz and 6 hertz at the same site \((F(5,75) = 4.3, P = .01)\). In contrast, occipital alpha measured as the average power in a 1-hertz band around the peak frequency in the 8-hertz and 12-hertz range at Oz was significantly attenuated by extended wakefulness in the eyes-closed resting condition but not in the eyes-open resting condition \((F(5,75) = 4.61, P < .01)\). For both slow eye movements and EEG spectral measures during resting conditions, the observed changes paralleled those observed in the subjective ratings, with no significant differences obtained between the 11:00 PM interval and the 12:00 PM baseline, a significant difference from baseline occurring by 1:30 AM, remaining at that level throughout the rest of the test session.

Impact of Sleep Loss on Behavior Measures during Task Performance

To examine changes in task performance over the course of the extended-wakefulness session, stimulus classification accuracy was characterized in terms of the ability to detect match trials as characterized by \(d'\)\(^ {62}\). Reaction times were measured in milliseconds and then log normalized prior to statistical analyses. Across test intervals, subjects responded more accurately \((F(1,15) = 38.22; P < .001)\) and faster \((F(1,15) = 53.58; P < .001)\) in the low-load task than in the high-load task (Figure 4). These effects of task load did not interact with test interval. Classification accuracy was approximately 15% lower late at night than during the 12:00 PM baseline \((F(5,75) = 4.90; P < .02)\), and reaction times were slowed on average by about 100 milliseconds \((F(5,75) = 6.53; P < .001)\). Independently of the overall slowing, reaction times also became relatively more variable over test intervals. That is, there was a significant increase in the “coefficient of variability” (computed for each subject as the ratio of the standard deviation of reaction times over trials within a block of trials to the average of reaction times within the block) over test intervals \((F(5,75)=4.28, P < .007)\). There were no significant interactions obtained between task load and interval for accuracy, reaction time, or reaction-time variability. Across tasks, none of these measures significantly differed between the 12:00 PM baseline and the 11:00 PM test interval. Marginal impairment in performance could be observed by the 12:30 AM test interval, and performance reached a nadir by the 1:30 AM test interval. That is, performance in both the low-memory-load and high-memory-load tasks had become significantly impaired by a relatively early stage of the extended-wakefulness session. Performance remained at that degraded level through the remaining test intervals, with no further decrement between 1:30 AM and 5:00 AM.

To more carefully evaluate the pattern of errors observed during the course of the extended-wakefulness session, the rate of false match responses (1.8% overall) was compared with the rate of false nonmatch responses. Although there was a slightly higher incidence of false nonmatch response on average (2.2% overall), this difference did not reach significance \((F(1,15) = 3.0, P = .10)\), nor was there any interaction between type of false response made and test interval. Furthermore, there was no significant difference between the rate of errors of commission (false-positive match and nonmatch responses, 4% of all trials) and errors of omission (failures to respond in the time allowable, 5.2% of all trials) nor was there any interaction between these two types of errors and test interval (both \(F < 1\)). Finally, there was a high positive.
correlation between these two error types over participants and test intervals (Spearman rho = 0.69, P < .001).

Impact of Sleep Loss on EEG Spectral Measures during Task Performance

Figure 5 compares average power spectra in the low-load and high-load working-memory tasks. As noted in the introduction, past studies indicate that regional power spectral measures in the theta and alpha bands are sensitive to variations in the working-memory load imposed by continuous performance tasks like those employed herein. In particular, the theta rhythm at frontal midline sites tends to be enhanced with higher working-memory loads, whereas the alpha rhythm tends to be attenuated, particularly at parietal sites. Such tonic differences in EEG spectral composition between tasks that differ continuously in working-memory composition might be expected to reflect the integrity of attention-control mechanisms. That is, they would appear to index differences in the effort that subjects willfully make and sustain over the course of several minutes in response to variations in the demands of the task environment.

To quantify these phenomena for statistical analyses, the spectral power of the working-memory-load–sensitive frontal theta rhythm was measured at the peak frequency in a 5-hertz to 7-hertz band at frontal midline electrode site AFz. The power of the alpha rhythm was originally measured in both an 8-hertz to 10-hertz band and a 10-hertz to 12-hertz band at electrode site Pz. Preliminary analyses indicated no important differences between these two alpha-band measures in response to sleep loss, so they were collapsed into a single task-related parietal alpha measure. Mean spectral power for frontal midline theta and parietal alpha rhythms at each test interval is presented in Figure 6. As in prior studies, the power of the frontal midline theta rhythm was observed to be greater in the high-load task than in the low-load task (F(1,15) = 7.08, P < .02). In contrast, increasing working-memory load was associated with attenuation of power in the alpha band at parietal sites (F(1,15) = 47.25, P < .001). Neither of these signals displayed a test interval by task load interaction (both P values > 0.1), indicating that the magnitude of the task load effect on EEG spectral parameters did not significantly differ over the course of the test session.

Despite the lack of any interaction with task load, both the frontal midline theta measure (F(5,75) = .759, P < .001) and the parietal alpha measure (F(5,75) = 3.24, P < .04) displayed overall main effects of test interval. As can be seen in Figure 6, the absolute power of both signals was lower at the 11:00 PM test interval of the extended-wakefulness-test session than it was at either the 12:00 PM daytime baseline or at the late-night test intervals. Since this effect does not appear to be related to any consistent fashion to either the subjective or objective measures of sleepiness described above, or to the observed pattern of changes in the task-related behavior measures, it is unlikely that the transient signal attenuation at approximately 11:00 PM is related to the same factors responsible for those other changes. An alternative possibility is that the
Effect of Sleep Loss on Stimulus-Locked ERPs

Studies of extended wakefulness, and of medication use that alters alertness, have found that attention-related and decision-related components of the ERP tend to be affected by sleepiness. Several components of the ERP response in the current study appear to be associated with attention and decision making in that they varied systematically between correctly classified matching versus nonmatching stimuli, between task loads, or between stimuli and task loads. These components included: 1) an N170 recorded over parieto-occipital regions (Figure 7); 2) a central P215; 3) a “P300” or late positive component (LPC); and 4) a positive slow wave recorded over central and parietal regions (Figure 8). To quantify these phenomena for statistical analyses, ERP component peak latencies were measured with respect to the time of stimulus onset, and amplitudes were measured with respect to the average amplitude 200-millisecond prestimulus onset.

The amplitude of the N170 (as measured at lateral parieto-occipital electrode P8) had complex task correlates, displaying a significant task-load-by-stimulus-type interaction (F(1,15) = 11.07, P < .005). This interaction resulted from a lack of difference in N170 amplitude between the two task types for nonmatch stimuli, whereas for match stimuli the N170 was much larger in amplitude in the low-load task than in the high-load task. The amplitude of the N170 (Figure 9, top) was attenuated over test intervals (F(5,75) = 7.46, P < .001), with a total increase of about 10 milliseconds between the 12:00 PM baseline measure and the 5:00 AM test interval. For both the amplitude and the latency measures, posthoc analyses revealed significant (P < .01) effects by the 1:30 AM test interval, with no further significant change over the remaining test intervals.

Peak amplitude of the P215 was larger for correctly classified nonmatch stimuli than for match stimuli (F(1,15)=8.26, P < .02), independent of task load. A significant main effect of test interval (Figure 9, middle) was also observed (F(5,75)=4.09, P < .01). There were no interactions between test interval and the other factors. As with the N170, relative to the 12:00 PM baseline, there was a significant (P < .01) reduction in P215 amplitude by the 1:30 AM test interval. This attenuation in amplitude persisted throughout the remainder of the session, though the P215 displayed a trend toward recovery at the 3:30 AM and 5:00 AM test intervals. No significant effects were observed for the peak latency of the P215.

Amplitude of the LPC (measured as the average amplitude in a 50-millisecond window around peak latency at parietal midline electrode Pz) did not display significant main effects of task load or stimulus type. There was, however, a significant interaction between these factors (F(1,15)=9.01, P < .01); in the low-load task, the LPC amplitude did not differ between match and nonmatch stimuli, whereas in the high-load task, the amplitude of this potential was much smaller to match stimuli than to nonmatch stimuli. A significant effect of test interval (Figure 9, bottom) was also obtained (F(5,75)=5.58, P < .04). As with the other ERP measures, posthoc analyses revealed that by the 1:30 AM test-interval amplitude of the LPC was significantly (P < .01) attenuated, and this attenuation persisted at approximately the same level throughout the remaining test intervals. Peak latency for the LPC did not significantly differ as a function of task load or of test interval.

The positive slow-wave component occurring at approximately 500 milliseconds to 600 milliseconds following stimulus onset (measured as the average amplitude in a 100-millisecond window around peak amplitude at parietal electrode Pz) was larger to correctly identified nonmatch stimuli than to match stimuli (F(1,15) = 22.68; P < .001), but it did not differ significantly over test intervals.

The behavior data reviewed above indicated that accuracy decreased and that reaction times increased and became more variable on a trial-by-trial basis (as measured by the coefficient of variability) in the late-night test sessions relative to the alert baseline. To examine whether there was a systematic relationship between these performance changes and the observed attenuation of ERPs with sleep loss, the change in LPC amplitudes between the daytime baseline measure and the extended-wakefulness session was calculated for each subject and test interval, and correlated with the corresponding change in the accuracy, response.
latency, and response-variability measures. The participants and test intervals that displayed the largest reduction in LPC amplitude also tended to display the largest decrease in response accuracy (Pearson r = 0.48, P < .001), the largest increase in reaction times (r = -0.42, P < .001), and the largest increase in response variability (r = -0.48, P < .001)

DISCUSSION

The objective of this study was to evaluate whether and how moderate sleep deprivation affects behavior and neurophysiologic measures of working-memory task performance. The extended-wakefulness manipulation induced significant sleepiness as measured with conventional subjective and electrophysiologic criteria. Even moderate levels of sleep loss were found to impair task performance and to disrupt neurophysiologic signals related to phasic aspects of working-memory task performance. These findings are discussed below.

Effects of Sleep Loss on Overt Task Performance

Some recent research has suggested that 1 night of sleep deprivation is not enough to impair performance on tasks designed to assess higher cognitive functions.70 However, most studies have found that modest amounts of sleep loss can significantly degrade performance on tests that explicitly incorporate a working-memory component or that otherwise are thought to require contributions from prefrontal cortical regions.71-74 Such deficits are consistent with the impairments in working memory and other executive functions that have been observed to accompany the sleep fragmentation and hypoxia associated with obstructive sleep apnea.75-77 The effects of sleep loss on behavior measures in the current study appear to be entirely consistent with such findings.

The observed effects of the working-memory-load manipulations on behavior data were in good agreement with previous findings17,26,27,29,30,32,33; accuracy was lower and reaction times were slower in the high-memory-load task than in the low-memory-load task. Of more interest to the current context, behavior began to degrade by the 12:30 AM test interval relative to the 12:00 PM alert baseline level. The beginning of this decline in overt performance was in good agreement with subjective measures of sleepiness. However, behavior reached a significant, asymptotic level of impairment by the 1:30 AM test interval. This rapid decline to an asymptotic level of functional impairment is in contrast to subjective sleepiness and to objective measures of alertness obtained from resting EEG data, which suggested that drowsiness continued to increase between the 1:30 AM and 5:00 AM test intervals.

Successful performance of the working-memory tasks demanded participants to sustain mental effort over several minutes, to strategically control and quickly focus their attention in order to accurately register transient stimulus events, and to rapidly compare incoming information to that maintained in working memory. The behavior data demonstrate that some critical aspect of this ability was significantly impaired when wakefulness was extended just an hour past the normal time of sleep onset. This result is consistent with the notion that even moderate amounts of sleep loss might increase the likelihood of performance errors in real-world activities—especially those that require sustained attention and working memory. Indeed, the magnitude of the behavior impairment observed herein when subjects were performing tasks just a few hours after their normal time of sleep onset exceeded that observed following a legally intoxicating dose of alcohol in these same subjects,34 and in other groups of subjects performing the same tasks.33,35 This observation is consistent with other reports that have compared the effects of sleep deprivation and alcohol on performance.66,78,79 In contrast, the magnitude of the behavior impairment associated with moderate sleep loss was not as great as that observed following a single standard 50-milligram dose of the over-the-counter antihistamine diphenhydramine in the same subjects.34

Tonic Modulation of the Ongoing EEG by Sleepiness and Sustained Men-
The Impact of Extended Wakefulness on the Phasic ERP

Careful analyses of behavior measures during sleep deprivation have led some researchers to posit that sleep loss produces an unstable mental state that is characterized by momentary lapses in attention and alertness. Such lapses lead to performance errors and an increase in the variability of response times that is disproportional to what might be expected from overall behavior slowing. In the current study, evidence of such “state instability” was provided by the observation of decreased accuracy on even the low-load version of the working-memory task, as well as a significant increase in the coefficient of variability measure of reaction times over the course of the extended-wakefulness session. Such drowsiness-related increases in error rate and response variability have been reported to be associated with a decrease in the transient electrodermal orienting response, an autonomic measure of the degree to which a stimulus is successful at capturing an individual’s attention.

Measures of the spectral power of the continuous EEG over a set of task trials—such as those described in the previous section—reflect the relative commitment of attention and working-memory resources to task performance over the course of several minutes. While adequate for characterizing tonic states and for differentiating the overall resource demands of tasks that vary in terms of the effortful attention required for their performance, such measures are likely to be poor indexes of subtle changes in more phasic aspects of attention, such as those required for perceptually analyzing a transient stimulus and for working-memory encoding and updating. In contrast, subsecond neurophysiologic measures such as stimulus-locked ERPs can be highly sensitive to any changes in the manner in which attention is transiently captured and focused in response to a stimulus event. Past research has demonstrated that such measures are affected by sleep deprivation and mental fatigue, and the ERP results from the present study are consistent with the notion that even moderate sleep loss can compromise more phasic aspects of attention.

For example, the N170 of the visual ERP has frequently been shown to be modulated by the strategic transient focusing of attention. That is, it is enhanced when stimuli are presented at a target location to which subjects are directing their attention and is attenuated when stimuli are presented away from the target location. Although the task used here differs from the classic visual attention task in which attention is manipulated by cues prior to each stimulus, the N170 in the current study also appeared to be enhanced by the strategic phasic focusing of attention. In particular, in the tasks employed here, subjects were required to compare stimulus to a target location indicated on a previous trial; this requirement produced an enhancement of the N170 response to stimuli that then occurred at the anticipated location, a result that replicates similar findings from other studies employing these tasks. With extended wakefulness, the N170 latency increased and N170 amplitude was significantly reduced. Thus, moderate sleep loss appeared to rapidly degrade a neural signal related to the selective focusing of attention onto particular stimulus attributes.

Similarly, past research has also indicated that ERP components corresponding to the P215 and the LPC are sensitive to the attention and working-memory requirements of a task. In the current study, these potentials also differed between stimuli that matched or failed to match the target stimulus in working memory, and, in the case of the LPC, this match sensitivity interacted with working-memory load. Extended wakefulness had a similar impact on the amplitude of these potentials as it did on the N170: both rapidly declined in amplitude when task performance was required after the participants’ normal time of sleep onset. These effects contrast with the lack of a significant attenuation for the parietal slow wave that followed the LPC. The lack of a slow wave effect suggests that extended wakefulness had its primary impact on components of the stimulus-locked neural response that are primed by selective attention to stimulus processing rather than ERP components related to subsequent operations.

Like the change in behavior measures, the overall average timecourse of the ERP changes also showed a rapid decline to an asymptotic floor between the 11:00 PM and 1:30 AM test intervals. Furthermore, correlation analyses indicated that there was a tight coupling between the size of the ERP amplitude attenuation observed in individual participants and test intervals over the course of the extended-wakefulness session and the magnitude of the performance impairments observed in those same participants and test intervals. Other investigators have observed similar correlations between the magnitude of ERP attenuation and the behavior impairments that are associated with sleep deprivation.

The amplitude of an averaged stimulus-locked ERP might decrease either as a result of the latency of the neural response to the stimulus becoming more variable across individual task trials or as a result of a decrease in the average absolute magnitude of the neural response produced across trials. The observed negative correlation between the ERP amplitude reduction and the increase in variability in reaction-time measures provides some indirect evidence that the former mechanism might be at least partly responsible for ERP-amplitude attenuation in response to sleep loss. However, this does not exclude the second possibility from also being a contributing factor, and other considerations are consistent with the notion that sleep loss is associated with a decrease in the magnitude of transient cortical responses. For example, in primate models, noradrenergic locus coeruleus neurons have been shown to display continuous moderately irregular activity during the alert waking state, punctuated by phasic enhancements of firing in the first 200 milliseconds following a task-relevant or attention-capturing stimulus. While the magnitude of locus coeruleus background activity might be associated with the animal’s general state or level of wakefulness, the phasic enhancement is thought to provide a brief, stimulus-specific modulating input to cortical networks and to produce a transient attention-related increase in the amplitude of the cortically generated ERP that follows task-relevant stimuli. Simulation studies suggest that this phasic cortical input from the locus coeruleus is also a critical factor in the animal’s ability to make fast and accurate responses. Drowsiness and decreased vigilance tend to be accompanied by a reduction in stimulus-related phasic enhancement of locus coeruleus neuronal activity and a contemporaneous deterioration of task related behavior. Such reduction of phasic noradrenergic input to the cortex might have played a central role in both the degraded behavioral performance and the reduced ERP amplitudes that were observed to occur in response to sleep loss in the current study.

Detecting Changes in Functional Alertness with Multivariate Methods that Combine Behavior and EEG Measures

As noted above, the data described here were collected as part of a larger study in which the same subjects also participated in four separate daytime test sessions in which they performed the same tasks before and after ingesting alcohol, caffeine, an antihistamine, or placebo. The average of the data from the premedication period for each of those sessions comprised the 12:00 PM baseline reference period for the sleep-deprivation manipulation. In analyses of the drug-effects data, multivariate methods (in particular, stepwise linear discriminant analysis) were applied to combinations of behavior and EEG variables to detect and quantify the neurocognitive effects of the drugs and to track their pharmacodynamics. Inclusion of EEG variables in discriminant functions led to more sensitive detection of drug effects than that which could be accomplished when only behavior performance variables were used. To begin to determine whether such methods could be extended to the problem of detecting changes in cognitive function associated with sleep deprivation, stepwise linear discriminant analyses were performed in which functions were derived (either from behavior measures alone, electrophysiologic measures alone, or from combinations of behavior and electrophysiologic measures) to discriminate each testing interval during the extended-wakefulness session from the 12:00 PM alert baseline data. A leave-out-one resampling procedure was used for cross-validation. In this approach, functions are iteratively developed on N-1 of
Figure 10 summarizes the results of the cross-validation analysis, illustrating the percentage of individuals (out of 16 total) detected as different from the alert baseline test interval at each night-time test interval for each of the three analysis strategies. Consistent with the univariate analyses, none of the three analysis strategies significantly discriminated data recorded at the 11:00 PM interval from the 12:00 PM baseline. By 12:30 AM, the behavior changes could be significantly detected (binomial P < .01), but analyses based on behavior alone did not yield a stable pattern of results when viewed over subsequent test intervals. Electrophysiologic changes from baseline could be detected in 100% of the participants by the 1:30 AM test session (P < .0001); however, as with behavior, analyses based on electrophysiologic measures alone provided a mixed picture when viewed across test intervals. In contrast, analyses that incorporated both behavior and electrophysiologic measures displayed a monotonic increase in discriminability from baseline, with the largest increase occurring between the 12:30 AM and 1:30 AM test intervals. By the 5:00 AM test interval, 94% of the data samples in the combined analysis could be accurately discriminated from baseline (binomial P < 0.0005), versus only 69% when behavior measures alone were used (P < .10). Such results indicate that the fairly modest amounts of sleep loss incurred in the current study were sufficient to induce neurocognitive changes that could be detected reliably in individual subjects. They further indicate that, as with analogous assessments of the psychoactive effects of pharmaceutical interventions, improved sensitivity in detecting such neurocognitive changes can be achieved when neurophysiologic measures are added to behavior measures in multivariate classification functions.34

CONCLUSIONS

Together, the results are consistent with the notion that even moderate sleep loss can compromise the function of neural circuits that support working memory and the strategic focusing of attention, decreasing the efficiency of rapid information processing and making performance more variable and error prone. The results complement recent imaging studies showing sleep-deprivation-related changes in cortical activation during attention and working-memory tasks,92-95 and extend these findings by providing information about the likely relative timing and phasic nature of such changes. Given the disruption to executive functions sometimes reported in patients with obstructive sleep apnea,75,76 the high sensitivity of neurophysiologic signals of attention and working-memory task performance to moderate degrees of sleep loss suggests that these types of measures might prove useful in assessing functional alertness in such patients.

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Figure 10—These results illustrate a multivariate method for detecting changes in an individual’s functional alertness relative to a baseline state. Each line indicates the percentage of data samples in each interval of the extended-wakefulness session correctly discriminated from the 12:00 PM alert baseline session, where each data sample represents the results from one subject at that test interval. The three lines reflect the relative cross-validation discrimination accuracies of mathematic functions consisting of weighted linear combinations of either behavior or electroencephalographic measures, or a combination of the two. For Ni-16, a discrimination accuracy of 75% or better is necessary to achieve a binomial significance of P < .05 or better. In the combined analyses, the binomial significance of discriminating data samples as coming from the night-time test session from the daytime baseline ranged from a low of P > .10 at the 11:00 PM test interval to a high of P < .0005 at the 5:00 AM interval.
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