Neurocognitive Consequences of Sleep Deprivation

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ABSTRACT

Deficits in daytime performance due to sleep loss are experienced universally and associated with a significant social, financial, and human cost. Microsleeps, sleep attacks, and lapses in cognition increase with sleep loss as a function of state instability. Sleep deprivation studies repeatedly show a variable (negative) impact on mood, cognitive performance, and motor function due to an increasing sleep propensity and destabilization of the wake state. Specific neurocognitive domains including executive attention, working memory, and divergent higher cognitive functions are particularly vulnerable to sleep loss. In humans, functional metabolic and neurophysiological studies demonstrate that neural systems involved in executive function (i.e., prefrontal cortex) are more susceptible to sleep deprivation in some individuals than others. Recent chronic partial sleep deprivation experiments, which more closely replicate sleep loss in society, demonstrate that profound neurocognitive deficits accumulate over time in the face of subjective adaptation to the sensation of sleepiness. Sleep deprivation associated with disease-related sleep fragmentation (i.e., sleep apnea and restless legs syndrome) also results in neurocognitive performance decrements similar to those seen in sleep restriction studies. Performance deficits associated with sleep disorders are often viewed as a simple function of disease severity; however, recent experiments suggest that individual vulnerability to sleep loss may play a more critical role than previously thought.

KEYWORDS: Sleep deprivation, neurocognitive, performance, neurobehavioral, sleep restriction, sleepiness, microsleeps, executive function, working memory, attention

Objectives: On completion of this article, the reader will be able to evaluate the effect of sleep deprivation on cognitive performance.
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SLEEP DEPRIVATION AND ACCIDENT RISK

Sleep deprivation increases the risk of human-error related accidents.[1] The overall prevalence of insufficient sleep in adults has been estimated at 20%.[2] The effects of insufficient sleep on cognitive processing is described below; however, the most common measure in population based studies is daytime sleepiness. A recent study to determine the prevalence of daytime sleepiness, using interviews over 5.5 years to follow 1007 randomly selected young adults age 21 to 30 years, was performed in southeast Michigan.[3] They found the average nocturnal sleep time during weekdays was 6.7 hours and on weekends was 7.4 hours. Sleepiness was inversely proportional to hours slept, and difficulty falling asleep was more prevalent in single adults with a full-time job. Studies in young adults indicate that 8 to 9 hours of extended nocturnal sleep are needed to resolve sleepiness caused by decreased sleep time.[4,5] The apparent chronic partial sleep deprivation of the young adults surveyed in 1997 complements statistics that find young drivers, especially males, at much higher risk for drowsy driving and sleep-related crashes.[6–8]

Accidents related to sleep deprivation have been estimated to have an annual economic impact of $43 to $56 billion.[9] Motor vehicle accidents related to fatigue, drowsy driving, and falling asleep at the wheel are particularly common but often underestimated.[10,11] Increased time awake, nocturnal circadian phase, reduced sleep duration, prolonged driving duration, and use of soporific medications have all been found to contribute to the occurrence of drowsy-driving and fatigue-related motor vehicle crashes.[6,12,13] Studies of shift workers,[14–16] truck drivers,[17–19] medical residents,[20–22] and airline pilots[23–26] show an increased risk of crashes or near misses due to sleep deprivation.

Sleepiness-related motor vehicle crashes have a fatality rate and injury severity level similar to alcohol-related crashes.[6] Sleep deprivation has been shown to produce psychomotor impairments equivalent to those induced by alcohol consumption at or above the legal limit.[27] For example, in a study of simulated driving performance, impairments in lane-keeping ability after a night without sleep were equivalent to those observed at blood alcohol content (BAC) of 0.07%.[28] Similarly, a study of professional truck drivers found that deficits in performance accuracy and reaction time at 28 hours of sleep deprivation were equivalent to those found after alcohol intoxication (BAC at 0.1%).[29] It appears that as continuous daytime waking exceeds 16 hours, psychomotor performance deficits increase to levels equivalent to BACs between 0.05 and 0.1%.[27,29]

Sleep deprivation poses a risk to safe operation in all modes of transportation and to performance in other safety-sensitive activities. By studying the impact of sleep deprivation on cognitive abilities, investigators have revealed plausible neurocognitive explanations for the observed behavioral decrements in different operational environments.

SLEEP DEPRIVATION AND SLEEP-WAKE REGULATION

An understanding of the effects of sleep deprivation on human neurobehavioral functions has improved as the neural systems controlling circadian and sleep homeostatic mechanisms have been identified.[23,30–32] Although much is known about the neurobiology of hypothalamic mechanisms involving sleep-wake regulation, much less is known about how these systems interact and alter waking neurocognitive functions. It is clear that both wakefulness and sleep are modulated by an endogenous biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The impact of the biological clock goes beyond compelling the body to fall asleep and to wake up again. The biological clock also modulates waking behavior, as reflected in sleepiness and cognitive performance, generating circadian rhythmicity in almost all neurobehavioral variables investigated.[33,34] Theoretical conceptualizations of the daily temporal modulation of sleep and wakefulness (and to a lesser extent the modulation of waking cognitive functions) have been instantiated in the two-process mathematical model of sleep regulation[35,36] and many mathematical variants of this model.[37] The two-process model of sleep regulation has been applied to describe the temporal profiles of sleep and wakefulness.[33,34] The model consists of a sleep homeostatic process (process S) and a circadian process (process C), which interact to determine the timing of sleep onset and offset, as well as the stability of waking neurocognitive functions.[33,34,38] The homeostatic process represents the drive for sleep that increases during wakefulness and decreases during sleep. When this drive increases above a certain threshold, sleep is triggered; when it decreases below another threshold, wakefulness is invoked. The circadian process represents daily oscillatory modulation of these threshold levels. The circadian drive for wakefulness may be experienced as the spontaneously enhanced alertness in the early evening even after a sleepless night. On the other hand, deprivation of sleep can elevate homeostatic pressure to the point that waking neurocognitive functions will be degraded even at the time of peak circadian drive for wakefulness.[39]

SLEEP PROPENSITY

Sleep deprivation increases sleep propensity, measured by polysomnography (PSG) as a reduction in the latency to sleep onset,[40] as well as shortening of the latencies from lighter stages of non-rapid eye movement (REM) sleep to deeper slow wave thalamocortical oscillations.[41]

For example, after a night without sleep, the daytime sleep latency of a healthy adult decreases, by an order of magnitude, to less than a minute or two on average, and the subsequent latency from sleep onset to slow wave sleep is halved.[41] Sleep latency, as a physiological measure of sleepiness, has been standardized in the multiple sleep latency test (MSLT).[40,42] Results on the MSLT may vary for many reasons, including prior sleep efficiency, prior sleep time, drug effects, physical activity, and posture.[43,44] A variant of the MSLT is the maintenance of wakefulness test (MWT), which also uses sleep latency to measure sleep propensity, but asks subjects to remain awake rather than fall asleep.[45] Like the MSLT, the MWT shows reduced sleep latency in response to sleep deprivation. Thus, whether attempting to sleep or resist sleep, the latency from waking to sleeping is reduced by sleep deprivation.

Microsleeps and Wake State Instability

The increased propensity for sleep to occur quickly, even when being resisted by the sleep-deprived subject, is consistent with evidence suggesting that "microsleeps" intrude into wakefulness when sleep-deprived subjects fail to respond (i.e., lapse) during cognitive performance demands.[46–49] Cognitive performance variability involving both errors of omission (i.e., behavioral lapses evident as failure to respond in a timely manner to a stimulus) and errors of commission (i.e., responses when no stimulus is present or to the wrong stimulus) are hallmarks of sleep deprivation.[50] Such variability during performance in sleep-deprived subjects has been hypothesized to reflect wake state instability.[39] The difference between the lapse hypothesis and the state instability hypothesis is in the explanation for the variability in cognitive performance during sleep deprivation. The lapse hypothesis posits that cognitive performance during sleep deprivation is essentially "normal" until it becomes disrupted by lapses or brief periods of low arousal.[49] In contrast, the state instability hypothesis[39] posits that variability in neurocognitive performance increases as homeostatic sleep-initiating mechanisms become progressively more disregulated with sleep loss. Thus, the brain's capacity to maintain alertness is hindered by the irrepressible activation of sleep processes.

Wake state instability occurs when sleep-initiating mechanisms repeatedly interfere with wakefulness, depending on the severity of sleep deprivation, making cognitive performance increasingly variable and dependent on compensatory mechanisms.[51,52] The ability of the sleep-deprived subject to engage in motivated behavior (e.g., walking) to compensate for or mask the cognitive effects of sleep loss is well recognized.[53,54] However, the compensatory effort to resist sleep ultimately cannot prevent intrusions of sleep initiation into wakefulness. In addition to reports of sleep-deprived subjects "semidreaming" while engaged in verbal cognitive tasks,[55,56] there are first-person reports of healthy sleep-deprived people falling asleep while ambulating in dangerous environments.[57] Thus, state instability evident in the cognitive performance and biobehavioral signs (e.g., slow eyelid closures[58–62]) of sleep-deprived subjects, as reflected by the occurrence of microsleeps or sleep attacks, is directly related to the increased variability in cognitive performance. The concomitant increase in errors of commission likely reflects an increased compensatory effort to resist sleep. It is also noteworthy that cognitive errors of omission and of commission during sleep loss increase with time on task. This finding is consistent with the process S/C interaction model of the homeostatic drive for sleep and endogenous circadian pacemaker.[39] Therefore, wake state instability means that at any given moment in time the cognitive performance of the sleep-deprived individual is unpredictable and a product of interactive, reciprocally inhibiting neurobiological systems mediating sleep initiation and wake maintenance. Theoretically, wake state instability suggests that there are multiple, parallel mechanisms by which waking and sleep states can interact. This is consistent with reports of the growing number of candidate molecules that may be involved in the co-occurrence of sleep and waking.[31]

Cognitive Performance During Sleep Deprivation

It has long been established that sleep deprivation degrades aspects of neurocognitive performance.[50,55,63] The first published experimental study of the cognitive performance effects of sleep deprivation on humans was reported in 1896 and involved three adults experiencing 90 hours of continuous wakefulness.[54] Since that time, many studies designed to measure behavioral changes associated with sleep deprivation have been performed. Analysis of the literature reveals three general types of studies: long-term total sleep deprivation (>45 hours); short-term total sleep deprivation (≤ 45 hours); and partial sleep deprivation (sleep restriction to <7 hours/24 hours). There are literally hundreds of published studies of the effects of total sleep deprivation, but many fewer on the effects of partial sleep deprivation, and only a handful on the effects of chronic partial sleep restriction. Moreover, neurocognitive measures vary widely among studies. Three categories of measurement commonly used in sleep deprivation studies include cognitive performance, motor performance, and mood.[64] Virtually all forms of sleep deprivation result in increased negative mood states, especially feelings of fatigue, loss of vigor, sleepiness, and confusion. Although feelings of irritability, anxiety, and depression are believed to result from inadequate sleep, experimental evidence of these mood states following sleep deprivation in a comfortable

and predictable environment is lacking. On the other hand, these alterations in mood have been observed repeatedly when sleep deprivation occurs without regard for conditions.[65]

Meta-analysis suggests that the effects of sleep deprivation on feelings of fatigue and related mood states are greater than effects on cognitive performance or motor functions.[64] When all three measures are collapsed together, the mean functional level of any sleep-deprived individual is estimated to be comparable to the 9th percentile of non–sleep-deprived subjects.[64] Interestingly, mood and cognition were found to be more affected by partial sleep deprivation than total sleep deprivation. On average, partial sleep-deprived subjects performed two standard deviations below their non–sleep-deprived counterparts, and total sleep-deprived individuals fell within 1 standard deviation of non–sleep-deprived controls. One explanation for the larger effect of partial sleep deprivation is that measures used in these studies may have been more sensitive to sleep deprivation. Recent investigations indicate that total sleep deprivation results in much more demonstrable effects on behavior than partial sleep deprivation.[66,67]

Sleep deprivation induces a wide range of effects on cognitive functions (Table 1), although cognitive tasks vary considerably in their sensitivity to sleep loss. In general, regardless of the task, cognitive performance becomes progressively worse when time on task is extended; this is the classic "fatigue" effect that is exacerbated by sleep loss.[50,68] However, performance on even very brief cognitive tasks that measure speed of cognitive "throughput," working memory, and other aspects of attention have been found to be sensitive to sleep deprivation.[69] Two confounding factors that can obscure the effects of sleep loss on many cognitive tasks are intersubject variability and intrasubject variability.[51] For example, one person's poorest performance during sleep deprivation may be superior to the best performance of a non–sleep-deprived person. Similarly, someone may be cognitively diminished by sleep loss but continue to improve on a repeated task due to the effects of learning. A second problem with many research reports on the cognitive effects of sleep deprivation concerns the nature of the dependent variables selected for analyses. A failure to understand that sleep deprivation increases variability within subjects (i.e., state instability) and between subjects (i.e., differential vulnerability to the effects of sleep deprivation, discussed below) can mean that the effects of sleep loss are missed in cognitive measures because less sensitive metrics or data analyses are used.[70,71]

Table 1 Summary of Broad Cognitive Performance Effects of Sleep Deprivation

Involuntary microsleeps occur
Attention-intensive performance is unstable with increased errors of omission and commission
Cognitive slowing occurs in subject-paced tasks, while time pressure increases cognitive errors
Response time slows
Both short-term recall and working memory performances decline
Reduced learning (acquisition) of cognitive tasks
Performance requiring divergent thinking deteriorates
Response suppression errors increase in tasks primarily subserved by prefrontal cortex
Response perseveration on ineffective solutions is more likely
Increased compensatory effort is required to remain behaviorally effective
Tasks may be begun well, but performance deteriorates as task duration increases
There is growing neglect of activities judged to be nonessential (loss of situational awareness)

To provide an accurate and useful measure of performance during sleep loss and the dynamic expression of waking neurobehavioral integrity as it changes over time, neurocognitive assessments must be valid and reliable reflections of fundamental waking functions that are altered by sleep deprivation. Measures of attention, vigilance, and declarative memory are often used, with the dependent variable being reaction time. The psychomotor vigilance task (PVT),[72] a test of behavioral alertness via sustained attention demands, is free of aptitude and learning effects and sensitive to sleep loss, sleep pathology, and functioning at an adverse circadian phase. The task requires continuous attention to detect randomly occurring stimuli. Such simple but attention-demanding tasks have proven to be reliable, valid, and sensitive measures of sleep deprivation, suggesting that the neural mechanisms of attention are among the most susceptible to sleep deprivation. The ubiquitous effects of sleep deprivation on attention-rich tasks should be understood relative to evidence that the dorsolateral prefrontal cortex (PFC) is one of the critical structures in a network of anterior and posterior "attention control" areas. The PFC has a unique executive attention role in actively maintaining access to stimulus representations and goals in interference-rich contexts.[73]

More complex cognitive tasks involving higher cognitive functions have often been regarded as insensitive to sleep deprivation (see Harrison and Horne[63] for review). One reason for this view may be the types of complex neurocognitive tasks used in some sleep deprivation studies. In particular, the use of novel logic-based tasks results in little change following sleep loss. Rule-based deduction and critical thinking are the result of convergent skills used in concert. When tasks are made more divergent, such as multitasking and flexible thinking, sleep deprivation appears to have adverse effects on performance. Divergent skills involved in

decision making that are effected by sleep loss include: assimilation of changing information; updating strategies based on new information; lateral thinking; innovation; risk assessment; maintaining interest in outcomes; mood-appropriate behavior; insight; and, communication and temporal memory skills.[63] In one study utilizing divergent, complex skills, including visual temporal memory, confidence judgment, verb generation to noun presentation, and response inhibition, assessments were made in normal subjects from different age groups.[63] Performance on these cognitive skill areas was lower in older subjects, but when young subjects were evaluated after 36 hours of sleep deprivation, their performance declined to that of the elderly. The authors suggest that decrements in cognitive performance due to aging may be similar to the effect of sleep deprivation. Neurocognitive deficits in healthy aging have been attributed to deficits in the prefrontal cortex.[74] Efforts continue to experimentally engage the prefrontal cortex with specific cognitive tasks during studies of sleep deprivation.

Implicit to divergent thinking abilities is a heavy reliance on executive functions performed by the prefrontal cortex. Executive function can be defined as "the ability to plan and coordinate a willful action in the face of alternatives, to monitor and update action as necessary and suppress distracting material by focusing attention on the task at hand."[75] Many tasks thought to engage different aspects of executive function have been used in studies of sleep deprived individuals. Examples include the Wisconsin card-sorting task, the Tower of London task, Torrence tests of creative thinking, the Hayling sentence completion task, and Thurstone's verbal learning task (see Jones and Harrison[75] and Harrison and Horne[63] for reviews). Commonalities between tasks include reliance upon working memory and attention systems. Working memory involves the ability to hold and manipulate information and can involve multiple sensory-motor modalities. Tests may include presentation of visual, auditory, or tactile sensory information, which is utilized in a verbal, mathematical, or spatial memory function. Deficits in neurocognitive performance requiring working memory result in difficulty determining the scope of a problem due to changing or distracting information[76–79]; remembering temporal order of information[80,81]; maintaining focus on relevant cues[78,82–85]; maintaining flexible thinking[83,86]; taking inappropriate risks[87,88]; having poor insight into performance deficits[63,89,90]; perseverating on thoughts and actions[76,77,91–93]; and problems making behavioral modifications based on new information.[79,83,93] Sleep deprivation therefore appears to adversely affect prefrontal cortex–related executive attention and working memory abilities. Although executive functions clearly rely upon cortical activity, the role of subcortical systems (hypothalamus, thalamus, and brain stem) in purported prefrontal cortex-mediated deficits remains to be determined. Thus far, neurophysiological and functional imaging studies confirm that sleep loss affects prefrontal cortex activity.

Neurophysiological Measures of Cognition Following Sleep Deprivation

Metabolic activation studies[94–98] and neurophysiological studies[99–103] using attention and working memory tasks in humans suggest that a functional network between prefrontal cortex and posterior association cortices are linked to these behaviors. Cortical structures are thought to support attention; however, subcortical structures such as the thalamus and the tectum play an important role. Two separate but interdependent cortical systems of attention have been proposed on the basis of neuroimaging studies in humans and neurophysiological experiments in animals.[104,105] An anterior network including the prefrontal cortex, anterior cingulate, and basal ganglia is involved in the process of selective attention and the ability to "hold on-line" a memory for use in the immediate future (working memory). A posterior network including the superior parietal lobes, superior colliculus, and pulvinar is involved in switching attention from one target to another. Efferent projections from the prefrontal cortex to the anterior cingulate and afferent projections from the anterior cingulate to the superior parietal lobes connect the two systems.

The effect of sleep deprivation on metabolism and electrophysiological signals generated by the prefrontal cortex and posterior association cortices has been studied in humans during sleep deprivation. Regional brain activation studies reliant on metabolic fluctuations using positron-emission tomography (PET)[106,107] and functional magnetic resonance imaging (fMRI)[108–112] show changes in response to sleep deprivation. PET studies show a global decrease in glucose metabolism throughout cortical and subcortical regions during sleep deprivation. As subjects become impaired on cognitive tasks, a more specific decrease in glucose uptake occurs in the PFC, thalamus, and posterior parietal association cortices.[106] fMRI studies indicate that after 24 hours of total sleep deprivation, attention-demanding tasks demonstrate increases in thalamic activation.[108] This is thought to demonstrate a neuroanatomical correlate of increased "mental energy" during states of low arousal. Following 35 hours of total sleep deprivation, verbal working memory tasks, which usually show increases in left temporal activity, result in decreased temporal lobe activation and increased parietal lobe activation (Fig. 1).[109–112] Increases in parietal lobe activation are associated with preservation of working memory function. This suggests a possible neurophysiological mechanism for individual compensatory responses utilizing posterior cortical systems in the face of sleep

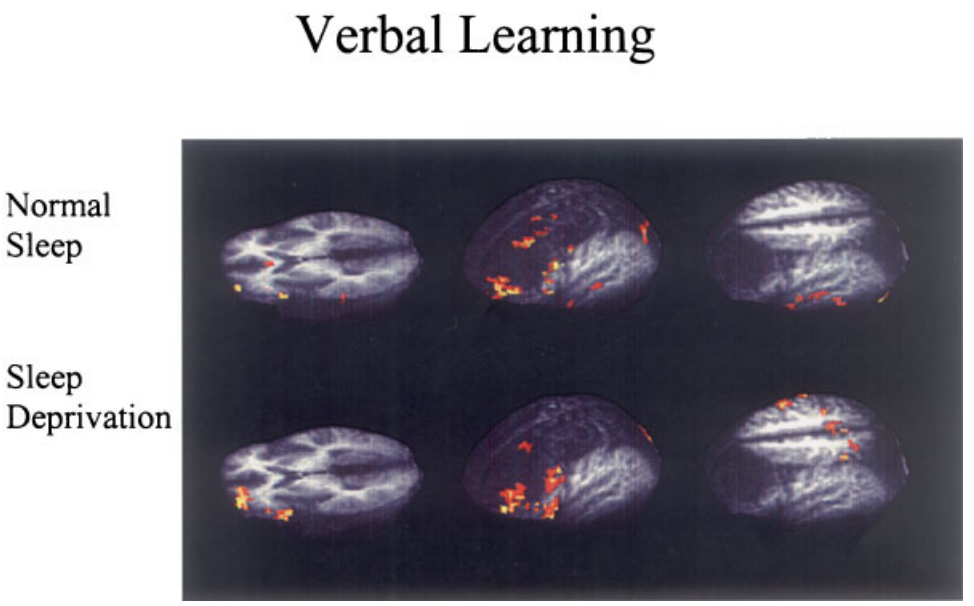

Figure 1 fMRI of regional brain activity during a verbal learning task following normal sleep (top row) and after 35 hours of total sleep deprivation (TSD) (bottom row). The two left columns show responses from individual nights that reached significance and the right column depicts between night analyses. The same 13 subjects were used to compile activation data for both groups, which were then overlayed onto a mean anatomical image. Colored regions correspond to clusters of significant activation; yellow = most intense, red = least intense. Axial images in the left column correspond to 2 mm above the anterior commisure–posterior commisure line. These images show responses in the prefrontal cortex (PFC) on both nights with an increase in spatial distribution following TSD. Sagittal images in the middle column show the enhanced spatial extent of PFC responses following TSD as well as a loss of temporal lobe activation with TSD. Sagittal sections in the right column demonstrate temporal lobe activation following normal sleep (top) compared with a loss of temporal lobe response and enhanced bilateral parietal lobe, right precentral gyrus, and precuneous activity after TSD (bottom). (Reprinted from Drummond SPA, Brown GG. The effects of total sleep deprivation on cerebral responses to cognitive performance. Neuropsychopharmacology 2001;25:S68–S73, with permission from Nature Publishing Group.)

deprivation. Although tantalizing, these studies are the first of their kind in sleep deprivation research, and continued investigation is needed.

Electroencephalography (EEG) signal-processing studies suggest that during sleep deprivation, performances on working memory and attention tasks are associated with tonic decreases in EEG amplitude of spectral features associated with alertness.[99,100,103] Phasic EEG changes associated with a stimulus result in event-related potentials (ERPs). Using a working memory task (the n-back) and the psychomotor vigilance task, investigators studied the effects of 21 hours of sleep deprivation on the tonic and phasic components of the EEG in humans.[113] Over the 21 hours, increasing subjective sleepiness (measured by the Karolinska Sleepiness Scale) was associated with increases in spectral slow wave activity in the parietal and occipital regions and simultaneous decreases in α frequency waveforms. Working memory performance showed a significant decline after 15 hours of wakefulness but did not decline further over the remainder of the 21 hours. Psychomotor vigilance task performance demonstrated the expected increased variability in reaction times over 21 hours and a 15% decrease in accuracy. A nadir in parietal α frequencies and an increase in frontal theta were associated with the significant decrease in working memory function. This suggests that as working memory function declined, a slowing in the PFC-posterior parietal system was observed. In addition, phasic ERP measures associated with attention and working memory tasks (N170, P215, and P300) showed significant increases in variability and a decline in amplitude following 15 hours of wakefulness. Amplitude decrements remained at a significantly lower level throughout the remainder of the 21-hour wake period.[113] Thus, the effect of extended wakefulness beyond 15 hours on working memory ability showed a functional neuroanatomic association with deficits in parietal and frontal lobe structures known to be involved in working memory and attention.

Neurocognitive Deficits in Chronic Partial Sleep Restriction

Although total sleep deprivation has proven a useful experimental paradigm for studying the neurocognitive effects of sleep deprivation, in reality it is a much less common form of sleep loss than partial sleep restriction. Chronic sleep restriction is common in modern society, due to a wide range of factors, including medical conditions, sleep disorders, work demands, and social and domestic responsibilities. Many early studies of chronic partial sleep restriction reported conflicting effects on cognitive performance (see Dinges et al[114] for a review). Recent studies, which have used neurocognitive tasks

sensitive to sleep deprivation and controlled factors that obscured accurate measurement of sleep restriction effects in the past, have found that 4 or more days of partial sleep restriction involving less than 7 hours sleep per night resulted in cumulative adverse effects on neurobehavioral functions.[66,67,115,116] Repeated days of sleep restriction to between 3 and 6 hours time in bed has been observed to increase daytime sleep propensity,[67,117] decrease cognitive speed/accuracy as reflected in working memory tasks,[66,67] and increase lapses of attention on the psychomotor vigilance task.[66,67,115,116]

In the most extensive, controlled dose-response experiment on chronic sleep restriction to date, the neurocognitive effects of 14 days of sleep limitation to no more than 4, 6, or 8 hours time in bed were compared with the effects of total sleep deprivation after 1, 2, and 3 nights without sleep.[66] Cognitive tasks, which were performed every 2 hours from 07:30 to 23:30 each day, included the psychomotor vigilance task, a working memory task, and cognitive "throughput" tasks. Subjective sleepiness was assessed and EEG recordings were continuously obtained for power spectral analyses. Three days of total sleep deprivation resulted in significantly larger deficits than any of the other three chronic sleep restriction conditions. No cognitive deficits occurred following 8 hours in bed for sleep each night. After 2 weeks of sleep restriction to 4 hours time in bed per night, deficits in attention, working memory, and cognitive "throughput" were equivalent to those seen after 2 nights of total sleep deprivation. Similarly, 2 weeks of restriction to 6 hours time in bed per night resulted in cognitive deficits equivalent to those found after 1 night of total sleep deprivation. The cumulative cognitive deficits increased in a nearly linear manner over days of 4 and 6 hours time in bed. Subjective sleepiness and fatigue ratings showed much smaller increases, suggesting an escalating dissociation between subjective perceptions of sleepiness and actual cognitive performance capability. Slow wave activity (delta power) in the sleep EEG also showed little response to chronic sleep restriction, in marked contrast to sleep EEG slow wave activity after total sleep deprivation. This is a particularly provocative finding, as it has long been assumed that slow wave sleep/EEG activity are associated with restorative sleep functions.[66,114] Apparently, as long as at least 4 hours of sleep time is permitted each night, slow wave activity does not reflect the homeostatic need for sleep during wakefulness. It would appear that some other aspects of physiological functions that occur in the second half of a typical 7- to 8-hour sleep period are essential for maintaining normal waking cognitive functions.

Another surprising aspect of two of the sleep restriction studies was the failure to find a linear relationship between the amounts of sleep that subjects lost over days (i.e., sleep debt) and the magnitude of the cognitive performance deficits. Cognitive deficits accumulated much more rapidly when no sleep was allowed than when the same amount of sleep was lost more gradually over days of sleep restriction.[66,67] Drake and colleagues[67] interpreted this as evidence of adaptation to chronic sleep loss, although Van Dongen and colleagues[66] suggested that the critical factor in producing daytime cognitive performance deficits was the cumulative amount of time subjects spent awake in excess of their usual wakefulness period (Fig. 2). This finding suggests that there is a critical period of stable wake time within each circadian cycle, after which neurocognitive deficits occur. They statistically estimated this critical period to be 15.84 hours, and its associated sleep period to be 8.16 hours, to prevent cumulative cognitive deficits in subjects.[66] Interestingly, the critical time period derived from this study closely matches the wake period that resulted in dramatic EEG changes in cortical areas associated with working memory.[113]

Collectively, sleep restriction studies suggest that cumulative deficits in cognitive functions are more likely to occur and to accumulate to significant levels when sleep in healthy adults is reduced below 7 hours per night.[114] However, as in total sleep deprivation experiments, this conclusion must be tempered by the fact that there are substantial interindividual differences not only in basal sleep need but also in resistance to and vulnerability to the cognitive effects of sleep loss.[118] Moreover, the latter may have little relationship to the former. There is now strong evidence that interindividual differences in cognitive deficits during sleep deprivation are systematic and traitlike, and the magnitude of these differences is substantial relative to the magnitude of the effect of prior sleep restriction.[118] Consequently, individual differences in neurocognitive responses to sleep deprivation are not merely a consequence of variations in sleep history. Rather, they involve traitlike differential vulnerability to impairment from sleep loss, for which neurobiological correlates have yet to be discovered.

Sleep Fragmentation: Experiments and Reality

Arousals during sleep are defined by PSG as abrupt increases in the EEG frequency for a minimum of 3 seconds during non-REM sleep and in association with increases in the electromyographic frequency during REM sleep.[119] By definition, arousals do not result in awakenings; however, they have been associated with excessive daytime somnolence,[120–127] cognitive performance deficits,[121,124,128–132] and mood alterations.[124,129,132,133] These studies show that sleep fragmentation has the same effect as sleep deprivation on waking behavior. Experimental sleep fragmentation models that use aural stimulation to produce transient

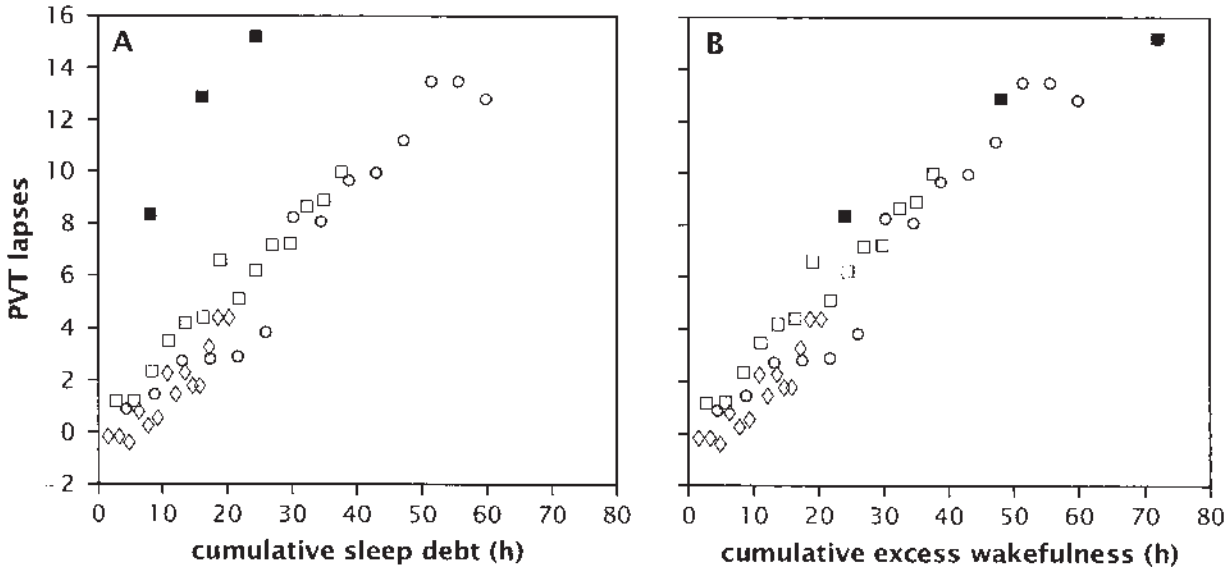

Figure 2 A graphic comparison of performance on a behavioral alertness test following 14 days of partial sleep deprivation (PSD) or 3 days of total sleep deprivation (TSD), as a function of cumulative sleep debt (left) or cumulative excess wakefulness (right). Alertness was measured by lapses on the psychomotor vigilance task (PVT). Cumulative sleep debt was determined by summating the difference between a statistically derived average sleep time of 8.16 hour/night and the actual hours of sleep each night (panel A). Cumulative excess wakefulness was determined by summating the difference between a statistically derived average daily wake time of 15.84 hour/day and the actual hours of wake each day (panel B). Each point represents the average time/day for each subject across 14 days of partial sleep restriction or 3 days of total sleep deprivation. Data from three PSD groups (8 hour = diamond, 6 hour = square, and 4 hour = open circle) and one TSD group (at days 1, 2, and 3 of TSD = solid square) are shown. Panel A illustrates a difference (nonlinear relationship) between behavioral performance in the PSD and TSD groups as a function of cumulative sleep debt. Panel B demonstrates a similarity (linear relationship) between behavioral performance in the PSD and TSD groups as a function cumulative excess wakefulness. The difference in analysis between panel A and panel B only affects the TSD condition since subjects who receive 0 hours of sleep per day build up a statistically estimated average sleep debt of 8.16 hours per day, but extend their wakefulness by 24 hours per day. Thus, panel B shows a monotonic, near-proportional relationship between cumulative excess wakefulness and neurobehavioral performance deficits. (Reprinted from Van Dongen HPA, 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 2003;26:117–126, with permission.)

changes in heart rate and blood pressure, but not EEG (or cortical) arousal, have demonstrated significant increases in daytime somnolence by MSLT and MWT.[134] In theory, one might expect waking neurocognitive deficits following the cumulative effect of multiple nights of sleep fragmentation. It is suggested that arousals occurring at a rate of 1 per minute lead to daytime cognitive impairments associated with 1 night of sleep deprivation.[121,135] This scenario may be all too common, especially when specific populations with intrinsic sleep disorders are considered.

Obstructive sleep apnea (OSA) is a common disorder affecting between 2 and 4% of the adult population[136–139] and is specifically addressed by another article in this series. Episodic obstructive apneas are associated with hypoxemia and cortical arousals. OSA-related arousals are related to increases in autonomic activity (heart rate and blood pressure) and may occur without cortical arousals.[134,140–142] Some investigators suggest that the severity of OSA due to hypoxemic neural damage may be related to deficits in executive function.[139,143,144] Reports indicate that neurophysiological measures, such as the P300 latency of the ERP in OSA patients, show slowing and amplitude changes consistent with sleep-deprived subjects.[145–148] These changes are noted to persist months after apnea reversal with continuous positive airway pressure.[147,148] Sleep fragmentation has also been linked to deficits in sustained attention tasks as well as excessive daytime somnolence.[123,124]

Neurocognitive deficits associated with OSA seem quite similar to those demonstrated following sleep deprivation and sleep fragmentation studies. A meta-analysis of cognitive dysfunction in sleep-disordered breathing patients was recently performed.[149] Twenty-eight studies met criteria for evaluation and revealed several neurocognitive deficits associated with this spectrum of disease. Moderate to large effect sizes were noted for performance on sustained attention tasks (i.e., Four Choice Reaction Time Test, PVT, and Continuous Performance Test), driving simulation, delayed visual memory retrieval, and working memory tasks requiring mental flexibility (i.e., Wisconsin Card Sorting Task [WCST] and Stroop interference trial). Verbal fluency tests showed small to moderate effect sizes, and short attention tasks (i.e., Trail Making Tests and Cancellation Tests), vigilance tests (i.e.; Mackworth Clock Performance and Parasumaran Vigilance Task),

delayed verbal retrieval tasks, and general intellectual function (i.e., full-scale IQ, WAIS-R estimated IQ, psychomotor efficiency factor, processing speed index, and Mini-Mental Status Exam) showed small effect sizes. No differences were found for reasoning tasks (i.e., WAIS-R Subtests Comprehension, Picture Arrangement and Picture Completion), concept formation (i.e., WAIS-R Subtest Similarities and WCST), and immediate visual or verbal memory tasks. Notably, there was not enough data to synthesize a quantifiable change in overall executive functions in sleep-disordered breathing patients. Thus, a rather startling array of deficits appears over a broad range of neurocognitive domains in OSA and sleep-related disordered breathing. The analysis points out several cognitive arenas that need further investigation including working memory and executive functions.

Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) represent two overlapping disorders that often lead to sleep fragmentation and excessive daytime sleepiness. Recent reports indicate that children with attention-deficit hyperactivity disorder (ADHD), symptoms suggestive of ADHD, or conduct problems have an increased incidence of RLS and PLMD.[150–155] Although attention deficits are easily demonstrable in these populations, it is unclear whether a cause-and-effect relationship between sleep fragmentation and cognitive deficits can be established. Although neurocognitive measures in RLS and PLMD are lacking, these disorders seem to offer a unique opportunity to study the effect of sleep fragmentation without hypoxemia on executive functions. Presumably, if cognitive deficits are found they may even be reversible given the availability of effective treatments such as dopaminergic therapy.

CONCLUSIONS

Sleep deprivation, whether from disorder or lifestyle, whether acute or chronic, poses significant cognitive risks in the performance of many ordinary tasks such as driving and operating machinery. Theories and hypotheses of how sleep deprivation affects neurocognitive abilities are evolving rapidly as both the range of cognitive effects from sleep loss and the neurobiology of sleep-wake regulation are better understood. For example, recent experiments reveal that following days of chronic sleep restriction, significant daytime cognitive dysfunction accumulates to levels comparable to that found after severe acute total sleep deprivation. Executive performance functions subserved by the prefrontal cortex in concert with the anterior cingulate and posterior parietal systems seem particularly vulnerable to sleep loss. Following wakefulness in excess of 16 hours, deficits in attention and executive function tasks are demonstrable through well-validated testing protocols. The destabilization of neurocognitive function following prolonged wakefulness may be due to alterations in both cortical and subcortical neural processing as demonstrated by neuroimaging and electrophysiological measures. Although neurophysiological processes show similar changes across human brains following sleep deprivation, individual performance of cognitive measures vary greatly in response to sleep deprivation, suggesting a traitlike (possibly genetic) differential vulnerability or compensatory changes in the neurological systems involved in cognition. Sleep-disordered breathing and nocturnal movement disorders show similar waking neurocognitive deficits to those seen in experimental sleep fragmentation protocols. Further studies of neurocognitive deficits in human disorders are needed as they impact large segments of the population.

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