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Neurocognitive Consequences of Sleep Deprivation

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Abstract

Sleep deprivation is associated with considerable social, financial, and health-related costs, in large measure because it produces impaired cognitive performance due to increasing sleep propensity and instability of waking neurobehavioral functions. Cognitive functions particularly affected by sleep loss include psychomotor and cognitive speed, vigilant and executive attention, working memory, and higher cognitive abilities. Chronic sleep-restriction experiments—which model the kind of sleep loss experienced by many individuals with sleep fragmentation and premature sleep curtailment due to disorders and lifestyle—demonstrate that cognitive deficits accumulate to severe levels over time without full awareness by the affected individual. Functional neuroimaging has revealed that frequent and progressively longer cognitive lapses, which are a hallmark of sleep deprivation, involve distributed changes in brain regions including frontal and parietal control areas, secondary sensory processing areas, and thalamic areas. There are robust differences among individuals in the degree of their cognitive vulnerability to sleep loss that may involve differences in prefrontal and parietal cortices, and that may have a basis in genes regulating sleep homeostasis and circadian rhythms. Thus, cognitive deficits believed to be a function of the severity of clinical sleep disturbance may be a product of genetic alleles associated with differential cognitive vulnerability to sleep loss.

Keywords

Neurobehavioral performance; sleep restriction; attention and executive function; functional neuroimaging; prefrontal cortex; thalamus; sensory processing areas; genetics

SLEEP DEPRIVATION AND ACCIDENT RISK

The overall prevalence of insufficient sleep in adults has been estimated at 20%.[1] The effects of insufficient sleep on cognitive processing are described below; of these, daytime sleepiness has been the most common measure assessed in population-based studies. One study determined the prevalence of daytime sleepiness using interviews conducted over 5.5 years which followed 1,007 randomly selected young adults ages 21 to 30 years in southeast Michigan.[2] That study 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.[2] Studies in young adults indicate that 8 to 9 hours of extended nocturnal sleep are needed to

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resolve sleepiness caused by decreased sleep time.[3,4] The apparent chronic partial sleep deprivation experienced by the young adults surveyed in 1997 complements statistics showing young drivers, especially males, are at much higher risk for drowsy driving and sleep-related crashes.[5–7]

Sleep deprivation increases the risk of human-error-related accidents,[8] with such accidents 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 all contribute to the occurrence of drowsy-driving-related and fatigue-related motor vehicle crashes.[6,12,13] Moreover, studies of shift-workers,[14–16] truck drivers,[17–19] medical residents,[20–22] and airline pilots[23–26] all show an increased risk of crashes or near misses due to sleep deprivation in these populations.

Sleepiness-related motor vehicle crashes have fatality rates and injury severity levels similar to alcohol-related crashes.[6] In addition, sleep deprivation produces 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 a blood alcohol content (BAC) of 0.07%.[28] Similarly, a study of professional truck drivers found that deficits in performance accuracy and reaction time after 28 hours of sleep deprivation were equivalent to those found after alcohol intoxication (BAC at 0.1%).[29] Thus, it appears that as continuous daytime waking exceeds 16 hours, psychomotor performance deficits increase to levels equivalent to BAC levels between 0.05% and 0.1%.[27,29]

Sleep deprivation poses risks to safe operation in all modes of transportation and to performance in other safety-sensitive activities.[30] Improved understanding of the neural basis of such risks in operational environments has been achieved through the experimental study of how precisely sleep deprivation affects discrete cognitive abilities.

SLEEP DEPRIVATION AND SLEEP–WAKE REGULATION

The identification of the neural systems controlling circadian and sleep homeostatic mechanisms has improved our understanding of the effects of sleep deprivation on human neurobehavioral functions.[23,31–33] Although much is known about the neurobiology of hypothalamic mechanisms involving sleep–wake regulation, less is known about how these systems interact and alter waking neurocognitive functions.[34,35] Both wakefulness and sleep are modulated by an endogenous biological clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Beyond driving the body to fall asleep and to wake up, the biological clock also modulates waking behavior, as reflected in sleepiness and cognitive performance, generating circadian rhythmicity in almost all neurobehavioral variables investigated.[34,35] 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[36,37] and in mathematical variants of this model.[38] The two-process model of sleep regulation has been used to describe the temporal profiles of sleep and wakefulness.[34,35] The model consists of a sleep homeostatic process (S) and a circadian process (C), which interact to determine the timing of sleep onset and offset, as well as the stability of waking neurocognitive functions.[34,35,39] 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 spontaneously-enhanced alertness in the early evening even after a sleepless night. Deprivation of sleep, however, can elevate homeostatic pressure to the point that waking cognitive functions will be degraded even at the time of the peak circadian drive for wakefulness.[40] The degradation of goal-directed cognitive behavior that can occur unpredictably in sleep-deprived individuals appears to reflect the transient intrusion of sleep neurobiology into waking neurobiology.[41]

Sleep Propensity

Sleep deprivation increases sleep propensity, measured using polysomnography, as a reduction in the latency to sleep onset,[42] as well as by shortening of the latencies from lighter stages of non-rapid eye movement (NREM) sleep to deeper slow wave thalamocortical oscillations.[43] 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.[43] The Multiple Sleep Latency Test (MSLT) standardized sleep latency as a physiologic measure of sleepiness.[42,44] MSLT results may vary for many reasons, including prior sleep efficiency, prior sleep time, drug effects, physical activity, and posture.[45,46] The Maintenance of Wakefulness Test (MWT), a variant of the MSLT, also uses sleep latency to measure sleep propensity, but requires subjects to remain awake (resist sleep) rather than fall asleep.[47] Like the MSLT, the MWT shows reduced sleep latency in response to sleep deprivation. Thus, whether attempting to fall asleep or resist sleep, the latency from waking to sleeping is significantly reduced by sleep deprivation.

Microsleeps and Wake State Instability

The increased propensity for sleep to occur quickly, even when being resisted by a 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.[48–51] 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) is a primary consequence of sleep deprivation.[40,52] Such variability during performance in sleep-deprived subjects has been hypothesized to reflect wake state instability.[40,41] According to this theory, two competing neurobiologic systems exert an influence on the behavior of a sleep-deprived individual. More rostral areas of the brain exert a top-down drive to sustain alertness (i.e., motivated behavior), while more central and caudal areas increase the involuntary homeostatic drive to fall asleep. The interaction of these drives results in unreliable behavior, including heightened moment-to-moment variability in cognitive functions. A hallmark feature of cognitive variability is lapsing (i.e., brief periods of half a second to many seconds of no response). Lapses are often so brief, they cannot be detected in behavior without a special test, such as the Psychomotor Vigilance Test.[41,53] As lapses increase in frequency, they increase in duration, and ultimately they can result in a full-blown sleep attack (i.e., no spontaneous recovery by the subject). Both acute total sleep deprivation and chronic partial sleep deprivation can produce a high rate of lapsing that ultimately progresses to full and sustained sleep onset during goal-directed behavior (e.g., motor vehicle operation).[8,41]

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.[51] By contrast, the state instability hypothesis[40] posits that responses between lapses can also slow and get worse with time on task, that errors of commission (wrong responses) can comingle with

errors of omission (lapses), and that variability in neurocognitive performance (more so than changes in average performance) increases as homeostatic sleep-initiating mechanisms become progressively more upregulated with sleep loss.[8,41] Thus, the brain's capacity to maintain alertness is hindered by the 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.[53,54] 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.[55,56] However, such a compensatory effort to resist sleep ultimately cannot prevent intrusions of sleep initiation into wakefulness. In addition to reports of sleep-deprived subjects "semi-dreaming" (likely hypnagogic reverie) while engaged in verbal cognitive tasks,[57,58] first-person reports exist of healthy sleep-deprived people falling asleep while ambulating in dangerous environments.[59] Thus, state instability evident in the cognitive performance and biobehavioral signs (e.g., slow eyelid closures[60–64]) of sleep-deprived subjects, as reflected by the occurrence of microsleeps or sleep attacks, is directly related to increased variability in cognitive performance. The concomitant increase in errors of commission can also reflect an increased compensatory effort to resist sleep (i.e., trying to stop lapses by overresponding). Both cognitive errors of omission and of commission during sleep loss increase with time on task.

The effects of sleep deprivation on wake state instability during cognitive performance means that at any given moment in time the cognitive ability of the sleep-deprived individual is unpredictable, and a product of interactive, reciprocally inhibiting neurobiologic systems mediating sleep initiation and wake maintenance. Theoretically, wake state instability suggests there are multiple, parallel mechanisms by which waking and sleep states can interact. This theory is consistent with reports of the growing number of candidate molecules that may be involved in the co-occurrence of sleep and waking.[32]

Cognitive Performance during Sleep Deprivation

It has long been established that sleep deprivation degrades aspects of cognitive performance.[52,57,65] The first published experimental study of the cognitive performance effects of sleep deprivation in humans was reported in 1896 and involved three adults experiencing 90 hours of continuous wakefulness.[56] Since 1896, many studies measuring behavioral changes associated with sleep deprivation have been performed. A review of the literature reveals three general types of studies: long-term total sleep deprivation studies (>45 hours), short-term total sleep deprivation studies (≤45 hours), and partial sleep deprivation studies (sleep restriction to <7 hours/24 hours). There are literally hundreds of published studies on the effects of total sleep deprivation, but far fewer on the effects of partial sleep deprivation, and only a handful on the effects of chronic partial sleep restriction. Moreover, the cognitive performance measures used vary widely among studies. Three categories of measurement commonly used in sleep deprivation studies include cognitive performance, motor performance, and mood.[66] 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 the existence of these mood states following sleep deprivation in a comfortable and predictable environment is thus far lacking. These alterations in mood, however, have been observed repeatedly when sleep deprivation occurs without regard for conditions.[67] On the other hand, self-reports of fatigue and sleepiness are often blunted in chronic sleep restriction relative to the more linear effects of chronic partial sleep loss on cognitive performance.[68]

An early meta-analysis suggested that the effects of sleep deprivation on feelings of fatigue and related mood states are greater than the effects on cognitive performance and motor functions.[66] This conclusion, however, appears to be the result of inadequate experimental controls and cognitive assessments in partial sleep deprivation studies conducted prior to 1997.[69] Experiments in the past 10 years have found that chronic sleep restriction results in more rapid cumulative increases in cognitive performance errors than subjective measures of fatigue and mood, and the effects are in proportion to the dose of sleep and chronicity of restriction,[68,70–73] although rapid versus gradual restriction of sleep can influence the rate of accumulation of cognitive deficits.[68,74]

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.[48,75] 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.[76] Two confounding factors that can obscure the effects of sleep loss on many cognitive tasks are intersubject variability and intrasubject variability.[53] For example, one individual’s poorest performance during sleep deprivation may be superior to that of the best performance of a non-sleep-deprived individual (this aptitude effect is the intersubject confound). Similarly, a person may be cognitively diminished by sleep loss, but continue to improve on a repeated task due to the effects of learning (this learning effect is the intrasubject confound). 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) can mean that the effects of sleep loss on cognitive measures are missed because less sensitive metrics or data analyses are used.[77,78]

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, cognitive assessments must be valid and reliable reflections of fundamental waking functions altered by sleep deprivation. As such, measures of attention, vigilance, and declarative memory are often used, with reaction time as the dependent variable. The Psychomotor Vigilance Test (PVT),[79] a measure of behavioral alertness via sustained attention demands, is free of aptitude and learning effects and sensitive to sleep loss,[41] sleep pathology, and functioning at an adverse circadian phase.[53,80] The PVT 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 is one of the critical structures in a network of anterior and posterior “attention control” areas. The prefrontal cortex has a unique executive attention role in actively maintaining access to stimulus representations and goals in interference-rich contexts.[81]

More complex cognitive tasks involving higher cognitive functions have often been regarded as insensitive to sleep deprivation (see reference 65 for a review), perhaps due to the types of complex neurocognitive tasks utilized in some studies. In particular, the use of novel logic-based tasks results in little change following sleep loss. When tasks are made more divergent, such as occurs with multitasking and flexible thinking, sleep deprivation has been reported to produce adverse effects on performance. Divergent skills involved in decision making that are affected 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.[65] 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.[65] Performance on these cognitive skill areas was poorer in older subjects, but when young subjects were evaluated after 36 hours of sleep deprivation, their performance declined to those levels of the older subjects. The authors suggest that decrements in cognitive performance due to aging may be similar to the effects of sleep deprivation. Neurocognitive deficits in healthy aging have been attributed to deficits in the prefrontal cortex.[82] Both aging and sleep deprivation appear to reliably slow cognitive "throughput."

Implicit to divergent thinking abilities is a heavy reliance on executive functions that require 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."[83] Many tasks believed to engage different aspects of executive function have been used in sleep deprivation studies. Examples include the Wisconsin Card-Sorting Task, the Tower of London Test, Torrance Tests of Creative Thinking, the Hayling sentence completion task, and Thurstone's verbal learning task (see references 65 and 83 for reviews). Commonalities among these 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 include presentation of visual, auditory, or tactile sensory information, utilized in verbal, mathematical, or spatial memory functions. Deficits in cognitive performance requiring working memory result in difficulty determining the scope of a problem due to changing or distracting information,[84–87] remembering the temporal order of information,[88,89] maintaining focus on relevant cues,[86,90–93] maintaining flexible thinking,[91,94] taking inappropriate risks,[95,96] having poor insight into performance deficits,[65,97,98] perseverating on thoughts and actions,[84,85,99–101] and having problems making behavioral modifications based on new information.[87,91,101]

Although there is evidence that sleep deprivation adversely affects prefrontal cortex-related executive attention and working memory abilities, these cognitive effects are often not nearly as conspicuous or easy to measure as those involving basic processes such as cognitive and psychomotor speed, and lapses. Moreover, although executive functions clearly rely upon cortical activity, the role of subcortical systems (hypothalamus, thalamus, and brainstem) in purported prefrontal cortex-mediated deficits remains to be determined. Functional neuroimaging studies confirm that sleep loss affects prefrontal cortex activity, but there is also evidence (reviewed below) that the thalamus and possibly other midbrain and brainstem nuclei have important roles in the mechanisms underlying cognitive performance deficits in sleep-deprived subjects.

Functional Neuroimaging after Acute Total Sleep Deprivation

Functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been increasingly used to examine the influence of sleep deprivation on brain metabolism and to relate changes in neural activity to behavioral performance decline and compensation (see references 102–105 for reviews). Among various domains of cognitive function, attention and working memory tasks predominate. These paradigms—mediated by reasonably well-understood brain networks involving the frontal and parietal cortices and subcortical structures including the thalamus and basal ganglia (see references 106–112 for reviews)—have been used to characterize the effects of sleep deprivation. Other tasks employed in neuroimaging studies on the effects of sleep deprivation include arithmetic calculation,[113–115] verbal learning,[116–118] logical

reasoning,[119] spatial navigation,[120] inhibition control,[121] risky decision making,[122] and emotional processing.[123]

PET STUDIES OF ACUTE TOTAL SLEEP DEPRIVATION

Wu and colleagues[124] conducted one of the earliest PET neuroimaging investigations exploring the effects of sleep deprivation on metabolism in the human brain. Their study used a continuous attention-demanding performance test and reported a significant reduction of absolute metabolic rates in the frontal and temporal lobes, thalamus, basal ganglia, and cerebellum without an overall decrease of whole brain metabolism following sleep deprivation. Greater reductions in absolute metabolic rates in the prefrontal cortex, thalamus, basal ganglia, and limbic regions after sleep deprivation were associated with greater deficits in vigilant attention as measured by reaction times. A more recent study from the same group, with an expanded number of subjects, replicated the findings that metabolism in the thalamus, basal ganglia, and frontal lobe decreases after 24 hours of sleep deprivation, and further reported that one night of recovery sleep only partially reversed metabolic reductions in these regions.[125] Using PET during the performance of serial addition/subtraction tasks that required both attention and arithmetic working memory, Thomas and colleagues[114,115] also found significant decreases in metabolic rates in the prefrontal cortex, anterior cingulate cortex, thalamus, and inferior parietal and temporal cortices across an 85-hour sleep deprivation period. The authors also reported that decreases in the thalamus, prefrontal cortex, and parietal cortices correlated with decreased cognitive performance and alertness over time.

Molecular tracers have also been used in PET studies to measure cerebral receptor changes following sleep deprivation. One study, using PET with F-18 CPFPX (8-cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine) to quantify cerebral A1 adenosine receptor binding (A1AR) before and after sleep deprivation, found that deprivation increased A1AR binding in the human brain, particularly in the orbitofrontal cortex.[126] Another study used PET with C-11 raclopride and C-11 cocaine radiotracers to measure dopamine D_2/D_3 receptors and transporters, respectively, and examined the effects of sleep deprivation on dopamine neurotransmission in the human brain.[127] Although sleep deprivation significantly decreased the specific binding of C-11 raclopride in the thalamus and striatum, which may reflect increases in dopamine cell firing and/or release after sleep deprivation, it did not change the binding of dopamine transporters in the striatum. A greater reduction in C-11 raclopride binding was associated with greater fatigue and sleepiness, and greater deficits in cognitive performance on visual attention and working memory tasks. The authors speculated that dopamine increases after sleep deprivation may underlie arousal maintenance in the presence of a greater homeostatic drive, but provide insufficient compensation for behavioral and cognitive impairment.[127]

fMRI STUDIES OF ACUTE TOTAL SLEEP DEPRIVATION

In contrast to PET, which requires the injection of invasive and rapidly decaying radioactive tracers, fMRI using blood oxygenation level dependent (BOLD) contrast is noninvasive, more cost effective, and easier to use. In addition to measuring tonic neural activation by comparing task and control conditions with a block design, BOLD fMRI can detect phasic hemodynamic responses to brief stimuli at a rate of up to once every 2 seconds by utilizing an event-related experimental design.[128] With event-related BOLD fMRI, researchers can pseudo randomly intermix stimuli of different types and categorize events post hoc on the basis of the subject's responses; this is necessary for studies to dissociate different performances during the same task conditions. Thus, BOLD fMRI has become the most

widely used imaging method for localizing regional brain function and, as such, is more applicable to sleep deprivation studies than PET.

Attention

Attention tasks appear to be particularly sensitive to sleep loss. For example, Portas and colleagues[129] used fMRI with a block design and measured brain activity during similar performance of a short attention task under different levels of arousal, including a normal level of arousal, a higher level of arousal induced by caffeine administration, and a lower level of arousal induced by sleep deprivation. They found that arousal level modulated activation in the thalamus, with greater activation after sleep deprivation, but did not modulate activation in the prefrontal cortex, anterior cingulate cortex, and parietal regions. Another study used event-related fMRI and measured brain activity using the Psychomotor Vigilance Test after a normal night of sleep and after 36 hours of total sleep deprivation.[130] Faster reaction times were related to increased activation within a sustained attention cortical network and subcortical arousal and motor systems. By contrast, slower reaction times (which can include lapses), particularly after sleep deprivation, were associated with greater activation in the frontal and posterior midline regions, which may reflect a failure to disengage the "default-mode network."[130]

A series of fMRI experiments using various tasks involving attention and memory have investigated the effects of sleep deprivation on functioning.[113,131–145] Converging evidence from some fMRI studies have largely replicated the effects of sleep deprivation on decreased neural activity observed in PET studies. For example, using a serial subtraction task, Drummond and colleagues[113] found decreased activation in the prefrontal cortex, parietal lobe, and premotor cortex after sleep deprivation. Choo et al[136] found reduced activation in the parietal lobe and left thalamus after 24 and 35 hours of sleep deprivation during the performance of verbal working memory tasks. Similarly, other studies have also found decreased activation in the prefrontal cortex and parietal regions during the performance of a verbal working memory task.[137,138] A replication study with two pairs of rested wakefulness and sleep deprivation scans, showed that brain activation patterns were highly correlated across sessions and the magnitude of decreased activation in parietal regions was preserved and correlated with behavioral decline after sleep deprivation.[142] Tomasi and colleagues[144] used a visual ball-tracking task and found decreased activation in the frontoparietal regions, but increased activation in the thalamus.

In a recent experiment on the effects of sleep deprivation on lapses during performance on a visual selective-attention task, Chee and colleagues[141] also found reduced activation in the frontoparietal regions during lapses in addition to decreased mean activation in these regions after sleep deprivation (Fig. 1).[141] Relative to lapses after a normal night's sleep, lapses during sleep deprivation were associated with the expected reduction in activity in frontal and parietal control, but also a marked reduction in visual sensory cortex activation, as well as reduced thalamic activation. The latter contrasted with elevated thalamic activation during nonlapse periods. Despite these differences, the fastest responses after normal sleep and after sleep deprivation "elicited comparable frontoparietal activation, suggesting that performing a task while sleep deprived involves periods of apparently normal neural activation interleaved with periods of depressed cognitive control, visual perceptual functions, and arousal."[141] These findings support the state instability hypothesis by providing evidence that neural changes are occurring rapidly and frequently in the brain when sleep-deprived subjects are attempting to maintain goal-directed behavior in the presence of elevated homeostatic sleep drive.

Verbal Learning

Utilizing novel multivariate techniques as opposed to traditional group- and voxel-wise analyses, two independent studies[132,134] identified decreased activation as a function of sleep deprivation, which correlated with memory performance decline in nonverbal and verbal recognition tasks. By contrast, other fMRI studies have found increased regional neural activity in the frontoparietal network following sleep deprivation, suggesting that a neurobiologic compensatory mechanism for behavioral and cognitive impairment results from sleep loss. For example, Drummond et al[116] reported increased activation in the prefrontal cortex and parietal lobe during the performance of a verbal learning task after 35 hours of total sleep deprivation. Greater parietal activation was associated with better memory performance on this task. When arithmetic subtraction was combined with verbal learning in a divided attention task,[131] fMRI results replicated increased activation in the prefrontal cortex, anterior cingulate cortex, and parietal regions, and showed a positive association between parietal activation and memory performance after sleep deprivation. Chee and colleagues[133] reported increased activation in the prefrontal cortex during the performance of a more complex verbal working memory task, but not during the performance of a simple working memory task after sleep loss. Sleep deprivation also increased prefrontal cortex and temporal activation during the performance of a complex spatial navigation task.[120] Similarly, Mander and colleagues[143] found increased parietal activation during covert attention orientation following sleep deprivation. In addition, by manipulating the verbal learning task with two levels of word difficulty, increased activation was observed in the prefrontal cortex and parietal lobe in response to difficult, but not easy words after 36 hours of sleep deprivation.[117] Moreover, using a logic reasoning task with parametrically manipulated levels of task difficulty,[119] stronger linear neural responses were observed in the prefrontal cortex and parietal lobe associated with increasing task demands after sleep deprivation.

Taken together, the neuroimaging findings suggest the effect of sleep deprivation on brain regions subserving different cognitive functions may not be universal, but rather dependent on cognitive demands and on the difficulty level of the specific tasks used in a study. In addition, more complex or difficult tasks appear to permit recruitment of additional neural resources as part of compensatory neurocognitive mechanisms, which may make these tasks less vulnerable to sleep deprivation. By contrast, tasks that rely heavily on vigilant attention, even when simple and easy to do—such as PVT performance or driving—appear to involve no recruitable compensatory neurobiology to maintain performance in most (but perhaps not all) individuals.

Memory Acquisition and Retention

Sleep deprivation impairs visual short-term memory and limits its capacity. A recent fMRI study[140] used parametrically manipulated perceptual or memory load in two visual tasks, and found that both tasks showed declines in behavioral performance and reductions in parietal and extrastriatal activation after sleep loss. Critically, sleep deprivation reduced the linear relationship between memory load and parietal activation at rested wakefulness. Moreover, cholinergic augmentation with donepezil reduced the negative effects of sleep loss on behavioral performance across both tasks and increased parietooccipital activation in a manner that correlated with performance in individuals who were vulnerable to sleep deprivation.[146] Attention lapses following sleep loss compared with those after normal sleep were associated with reduced activation in the visual sensory cortex and thalamus.[141]

Acute total sleep deprivation also produced a significant deficit in hippocampal activity during episodic memory encoding, resulting in worse subsequent retention.[118] Such findings suggest that a lack of sleep compromises the neural and behavioral capacity for committing

new experiences to memory, which is essential for learning. Functional connectivity analysis showed that sleep deprivation increased connectivity between the hippocampus and basic alertness networks of the brainstem and thalamus on a memory consolidation task.[118] Like other neuroimaging studies, these findings support the notion that lower brain areas involved in arousal, sensory/perceptual gating, and attentional functions contribute to impairments in memory following sleep deprivation. This conclusion was recently confirmed by a transcranial magnetic stimulation study showing that stimulation in the left lateral occipital cortex improved memory function after sleep loss.[147]

Emotional Memories and Emotional Processing

The role of sleep loss in consolidation of emotional (negative and positive) memories and in emotional processing has also been studied with fMRI.[123,145] In one study, sleep deprivation deteriorated recollection of both neutral and positive stimuli, but not negative stimuli.[145] Successful recollection of emotional stimuli elicited larger responses in the hippocampus and various cortical areas, including the medial prefrontal cortex, in the sleep group than in the sleep-deprived group.[145] When sleep deprived, recollection of negative items (but not positive items) elicited larger responses in the amygdala and an occipital area than when sleep was obtained.[145] Another study[123] used an emotional stimulus viewing task and demonstrated enhanced neural responses to negative stimuli in the amygdala and reduced functional connectivity between the amygdala and medial prefrontal cortex.

Expectations of Reward

The effects of a night of sleep deprivation on expectations of reward found that sleep loss elevated expectations of higher reward on a gambling task, as nucleus accumbens activation increased following risky choices, and it attenuated neural responses to gambling losses in the insular and orbito-frontal cortices.[122] However, sleep loss did not change behavioral performance on the gambling task, suggesting that neuroimaging may be more sensitive than behavior for detecting possible deficits in brain function following sleep deprivation.

INDIVIDUAL DIFFERENCES IN COGNITIVE VULNERABILITY TO ACUTE TOTAL SLEEP LOSS

Beyond task difficulty, interindividual differences may contribute to the inconsistent findings derived from functional neuroimaging studies. Behavioral studies have consistently reported large interindividual differences in cognitive responses to sleep deprivation, suggesting trait-like differential vulnerability[148] (see next section for further discussion). Most fMRI studies have used small samples (usually 10 to 30 subjects) and employed group-level analyses, both of which mask individual variation in a heterogeneous population. Several recent fMRI studies have examined brain activation patterns in subjects who appeared to be either cognitively more vulnerable versus less vulnerable to sleep loss. In one study, Mu and colleagues[138] compared brain activation between 10 more vulnerable and 10 less vulnerable young male subjects during performance of a working memory task at rested baseline (after normal sleep) and after sleep deprivation (when the vulnerability of subjects was defined based on their cognitive responses). Although both groups showed reduced frontoparietal activation after sleep deprivation, less vulnerable subjects showed significantly more activation both at rested wakefulness and after sleep deprivation. This finding is consistent with another working memory study that showed greater activation in left frontoparietal regions at rested wakefulness was associated with better memory performance after 24 hours of sleep deprivation.[139] The results from these two studies support the “cognitive reserve hypothesis,” which suggests that subjects who are less cognitively vulnerable to sleep loss may have more preexisting cognitive resources or a

greater capacity to engage alternative neural resources as demand increases during sleep deprivation.[149]

Unfortunately, results opposing this hypothesis have also been obtained. That is, better inhibition efficiency after sleep deprivation was associated with less activation in the right ventral prefrontal cortex at rested wakefulness using the go/no-go task.[121] Although several factors may account for the inconsistency of findings, it is noteworthy that all of these studies failed to prospectively phenotype subjects' cognitive vulnerability to sleep deprivation before imaging them, which would have helped separate state and trait variance in these experiments. Given these inconsistent findings, additional studies are needed to understand the neural mechanisms mediating trait-like differential cognitive vulnerability to sleep deprivation in normal individuals that has been carefully documented.[148]

Arterial Spin Labeled (ASL) Perfusion fMRI

Although findings from fMRI studies have significantly enriched our understanding of how sleep deprivation affects brain activation and how neural responses relate to cognitive and behavioral performance changes, several essential technical and methodological shortcomings of the BOLD contrast may limit its future application to sleep deprivation studies. BOLD contrast lacks absolute quantification and can only measure relative signal changes, which affects the accurate interpretation of observed sleep loss effects. Second, the presence of low frequency noise in the signal[150,151] decreases the sensitivity of BOLD fMRI for tracking slow neural activity changes for longer than a few minutes.[152,153] For this reason, BOLD imaging may be unsuitable for directly assaying sleep deprivation-induced neural activity changes occurring over a few days.

A recently developed neuroimaging technique—arterial spin labeled (ASL) perfusion fMRI—utilizes magnetically labeled arterial blood water as a diffusible tracer for blood flow measurements in a manner analogous to that used for 15O-PET scanning.[154,155] This technique provides a noninvasive imaging method to quantify cerebral blood flow (in mL/100 g per minute) during the performance of cognitive tasks[156–159] as well as during task-free resting states.[160–162] ASL-perfusion fMRI also offers reliable measures of cerebral blood flow with excellent reproducibility over long time periods.[153,163] These features suggest that ASL-perfusion fMRI may be a compelling method for functional imaging studies of sleep deprivation. Indeed, although no sleep deprivation study using ASL perfusion imaging has yet been published, preliminary data reported at scientific meetings[164,165] support the feasibility of this technique.

Cognitive Deficits from Chronic Partial Sleep Restriction

Although total sleep deprivation is a useful experimental paradigm for studying the neurocognitive effects of sleep deprivation, in reality it is a much less representative form of sleep loss than chronic 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.[70,71] Many early studies of chronic partial sleep restriction reported conflicting effects on cognitive performance (see references 70 and 71 for reviews). Recent studies—using neurocognitive tasks sensitive to sleep deprivation and controlling those factors that in prior studies obscured accurate measurement of sleep restriction effects—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.[68,72,73] Repeated days of sleep restriction to between 3 and 6 hours time in bed increased daytime sleep propensity,[73,166] decreased cognitive speed/accuracy as reflected in working memory tasks,[68,74] and increased lapses of attention on the Psychomotor Vigilance Test.[68,72,73]

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 in bed were compared with the effects of total sleep deprivation after 1, 2, and 3 nights without sleep.[68] Cognitive tasks, which were performed every 2 hours from 7:30 AM to 11:30 PM each day, included the Psychomotor Vigilance Test, a working memory task, and cognitive "throughput" tasks. Subjective sleepiness was assessed and electroencephalogram (EEG) recordings were continuously obtained for power spectral analyses. Three days of total sleep deprivation resulted in significantly larger deficits than any of the three chronic sleep restriction conditions. No cognitive deficits occurred following 8 hours time 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 two 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 one 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 slow wave activity after total sleep deprivation. This is a particularly provocative finding because it has long been assumed that slow wave sleep/EEG activity are associated with restorative sleep functions.[68,70] 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. Thus, other aspects of physiologic functions occurring in the second half of a typical 7-to-8-hour sleep period appear essential for maintaining normal waking cognitive functions.

Surprisingly, the two aforementioned sleep restriction studies failed to find a linear relationship between the amount 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.[68,74] Drake and colleagues[74] interpreted this finding as evidence of adaptation to chronic sleep loss, although Van Dongen and colleagues[68] suggested that the crucial 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: this statistically estimated critical period was equal to 15.84 hours, and its associated sleep period was equal to 8.16 hours.[68] There are as yet no published studies to establish whether the same neural responses occur when cumulative cognitive deficits from chronic sleep restriction reach levels comparable to the deficits induced by acute total sleep deprivation.

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.[70] 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 and vulnerability to the cognitive effects of sleep loss.[148] Moreover, the latter may have little relationship to the former. There is now compelling evidence that interindividual differences in cognitive deficits during sleep deprivation are systematic and trait-like, and the magnitude of these differences is substantial relative to the magnitude of the effect of prior sleep restriction.[148] Consequently, individual differences in neurocognitive responses to sleep deprivation are not merely a consequence of variations in sleep history. Rather, they involve trait-like

differential vulnerability to impairment from sleep loss, for which neurobiologic or genetic correlates have yet to be uncovered.

Genetics of Sleep Deprivation

The stable, trait-like interindividual differences observed in response to total sleep deprivation[78,148,167,168]—with intraclass correlations ranging from 58 to 92% for neurobehavioral measures[78,148]—strongly suggest an underlying genetic component. Until recently, however, the genetic basis of such differential vulnerability to sleep loss in normal healthy subjects has received little attention[169–171] despite active ongoing genetics research in other related areas. For example, several studies have investigated frequency differences of sleep and circadian genetic polymorphisms in clinical (e.g., major depression and bipolar disorder[172–175]) and nonclinical subjects.[176,177] Other studies have investigated specific genes involved in sleep and circadian rhythm sleep disorders, including insomnia, restless legs syndrome, narcolepsy, sleep apnea, and advanced and delayed sleep phase disorders (see references 178–180 for reviews).

By contrast, only a handful of studies have examined the role of human genetic polymorphisms on functioning in healthy subjects undergoing total sleep deprivation. One study found that the *Val158Met* polymorphism of catechol-*O*-methyltransferase (COMT) modulates the efficacy of modafinil on waking function, but neither this COMT genotype nor modafinil affected sleep-deprivation-induced changes in recovery sleep.[181] Another study from the same group reported an association between an A2A receptor gene polymorphism and objective and subjective differences in caffeine's effects on NREM sleep after total sleep deprivation.[182]

Three related studies investigated the role of the variable number tandem repeat (VNTR) polymorphism of the circadian gene *PERIOD3* (*PER3*)—which shows similar allelic frequencies in African Americans and Caucasians/European Americans[183,184] and is characterized by a 54-nucleotide coding region motif repeating in 4 or 5 units—in response to total sleep deprivation by using a small group of the same subjects specifically recruited for the homozygotic versions of this polymorphism. Compared with the 4-repeat allele, the longer, 5-repeat allele ($PER3^{5/5}$; $n = 10$) was associated with higher sleep propensity both at baseline and after total sleep deprivation, and worse cognitive performance, as assessed by a composite score of 12 tests, following total sleep deprivation.[185] A subsequent report—using the same 24 subjects—clarified that the $PER3^{5/5}$ overall performance deficits were selective: they only occurred on certain executive function tests, and only at 2 to 4 hours following the melatonin rhythm peak, from ~ 06:00 to 08:00.[186] Such performance differences are hypothesized to be mediated by sleep homeostasis.[185,186] Another publication on the same subjects showed that $PER3^{5/5}$ subjects had more slow wave sleep and elevated sympathetic predominance and a reduction of parasympathetic activity during baseline sleep.[187] These studies found no significant differences in the melatonin and cortisol circadian rhythms, *PER3* mRNA levels, or in a self-report morningness–eveningness measure,[185,186] although another study using these same subjects found *PER3* expression and sleep timing were more strongly correlated in $PER3^{5/5}$ subjects.[188] Other studies have shown that this polymorphism is associated with diurnal preference and delayed-sleep-phase syndrome.[189–192] Though compelling, these studies have yet to be replicated using independent, larger samples and thus should be considered preliminary. Indeed, we recently examined this genetic polymorphism and its relationship with cumulative neurobehavioral and homeostatic functions in chronic sleep restriction,[193] a condition more applicable to real world situations. We found that the *PER3* VNTR polymorphism was not associated with individual differences in neurobehavioral responses to chronic sleep restiction, although it was slightly but significantly related to one marker of sleep homoeostatic response during chronic sleep restriction. The *PER3* genotypes were

comparable at baseline and showed equivalent inter-individual vulnerability to sleep restriction indicating that *PER3* does not contribute to the neurobehavioral effects of chronic sleep loss.[193]

Sleep Fragmentation: Experiments and Reality

Arousals during sleep are defined by polysomnography as abrupt increases in the EEG frequency for a minimum of 3 seconds during NREM sleep and in association with increases in the electromyographic frequency during REM sleep.[194] By definition, arousals do not result in awakenings; however, they have been associated with excessive daytime somnolence,[195–201] cognitive performance deficits,[195,198,202–206] and mood alterations.[198,203,206,207] 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 changes in heart rate and blood pressure, but not EEG (or cortical) arousal, have demonstrated significant increases in daytime somnolence using the MSLT and MWT.[208] In theory, one might expect waking neurocognitive deficits following the cumulative effect of multiple nights of sleep fragmentation. It has been suggested that arousals occurring at a rate of one per minute lead to daytime cognitive impairments associated with one night of sleep deprivation.[195,209] This scenario may be all too frequent, 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.[210–213] Episodic obstructive apneas are associated with hypoxemia and cortical arousals. OSA-related arousals are associated with increases in autonomic activity (heart rate and blood pressure) and may occur without cortical arousals.[208,214–216] Some investigators suggest that the severity of OSA due to hypoxemic neural damage may be related to deficits in executive function.[213,217,218] Reports indicate that neurophysiologic measures, such as the P300 latency of the event-related potentials in OSA patients show slowing and amplitude changes consistent with sleep-deprived subjects.[219–222] These changes persist months after apnea reversal with continuous positive airway pressure.[221,222] Sleep fragmentation has also been linked to deficits in sustained attention tasks as well as excessive daytime somnolence.[197,198] More recently, investigations of OSA in adults[223] and children[224,225] demonstrate that sleep apnea creates a pro-inflammatory state, which may precipitate other important chronic medical conditions, such as hypertension, type 2 diabetes, obesity, metabolic syndrome, stroke, and heart failure. A relationship may also exist between such inflammation and neurocognitive dysfunction in apneic patients.[226,227] At present, therapies targeting the inflammatory response in OSA have not been assessed with respect to their effects on cognitive function.

Neurocognitive deficits associated with OSA appear quite similar to those demonstrated in sleep deprivation and sleep fragmentation studies. A meta-analysis of cognitive dysfunction in sleep-disordered breathing patients using twenty-eight studies revealed several neurocognitive deficits associated with this spectrum of disease.[228] Moderate to large effect sizes were noted for performance on sustained attention tasks (i.e., Four Choice Reaction Time Test, Psychomotor Vigilance Test, and Continuous Performance Test), driving simulation, delayed visual memory retrieval, and working memory tasks requiring mental flexibility (i.e., Wisconsin Cart Sorting Task 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., Mack-worth Clock Performance and Parasumaran Vigilance Task), delayed verbal retrieval tasks and general intellectual function (i.e., full-scale intelligence quotient [IQ], Wechsler Adult Intelligence Scale-Revised [WAIS-R] estimated IQ, psychomotor efficiency factor, Processing Speed Index, and Mini-Mental Status Exam) all 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 Wisconsin Cart Sorting Task) and immediate visual or verbal memory tasks. Notably, there was not enough data to identify a quantifiable change in overall executive functions in sleep-disordered breathing patients. Thus, a comprehensive array of deficits appears over a broad range of neurocognitive domains in OSA and sleep-related disordered breathing. This meta-analysis highlights several cognitive arenas that need further investigation in this population including working memory and executive function.

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), with symptoms suggestive of ADHD, or with conduct problems have a higher incidence of RLS and PLMD.[229–234] 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. Recent studies comparing untreated RLS patients with control populations demonstrate statistically and clinically significant deficits in standard measures of executive function (similar to deficits reported after one night of total sleep deprivation in controls).[235] In additional experiments, prefrontal cortex function was assessed in RLS patients and compared with controls who underwent two weeks of partial sleep restriction. The results demonstrated that RLS patients perform significantly *better* than sleep-deprived controls on executive function tasks, suggesting a possible adaptation to sleep deprivation in RLS patients.[236] Taken together, these data suggest that sleep deprivation alone (as assessed in control subjects) may not account for the observed deficits in executive function noted in RLS. Indeed, other factors such as periodic limb movements, arousals, and/or dopaminergic dysfunction also may play a role. Additional neurocognitive assessments in RLS and PLMD are needed because these disorders offer a unique opportunity to study the effect of sleep fragmentation without hypoxemia on executive function. Any detectable cognitive deficits may be reversible with effective treatments such as dopaminergic therapy.

CONCLUSION

Sleep deprivation, whether a result of a clinical disorder or lifestyle choices, and whether acute or chronic, poses significant cognitive risks in the performance of many ordinary tasks such as driving and operating machinery. Theories 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 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. Functional neuroimaging techniques indicate that wake state instability underlies many of the cognitive effects of sleep loss and involves sleep-promoting systems initiated during motivated behavior in which wake-promoting systems are active. Although neurophysiologic processes show similar changes across human brains following sleep deprivation, individual performance on cognitive measures vary greatly in response to sleep deprivation, suggesting trait-like (i.e., genetic) differential vulnerability or compensatory changes in the neurologic systems involved in cognition. New research has begun to investigate such possible genetic influences. 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 and following cumulative sleep restriction in healthy adults are needed. The results of such studies will have significant health implications for large segments of the population.

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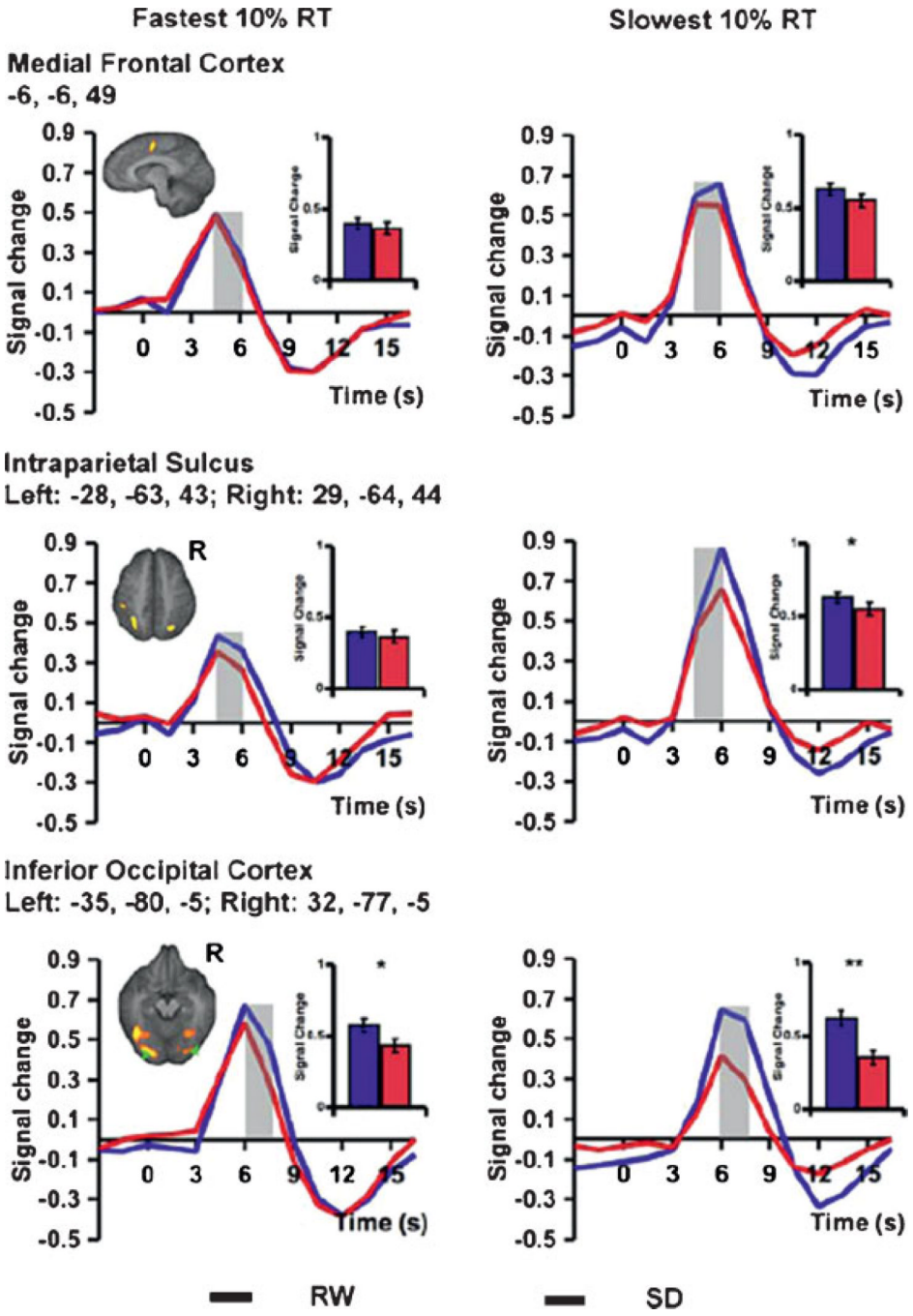

Figure 1.

Functional magnetic resonance imaging (fMRI) responses from three cortical areas during a visual, global/local selective attention task performed by $N = 24$ healthy young adults when not sleep deprived (RW, in blue) and when sleep deprived (SD, in red) for one night. The graphs display differential neural responses in the medial frontal cortex (top), bilateral intraparietal sulcus (middle), and bilateral inferior occipital cortices (bottom), in association with the fastest 10% reaction times (RT) (left column) and the slowest 10% RTs (right column). A threshold of $p < 0.001$ was used to detect task-related activation. For both RW and SD states, slower responses were associated with higher peak fMRI signals in the medial frontal cortex and bilateral intraparietal sulcus (all $p < 0.005$). When comparing SD

with RW, peak signal for the slowest 10% of trials was significantly lower in the parietal and occipital regions (right middle and bottom), but not in the medial frontal cortex (right top). SD also attenuated task-related thalamic activation (not shown). Peak signal in the occipital region after SD was significantly lower than RW even for the fastest 10% of trials (left bottom). However, there was no difference between RW and SD states in the frontal or parietal peak fMRI signals for the fastest responses across states (left top and middle). The shaded time points indicate those contrasted to assess significant state effects. The inset shows the mean peak signal associated with the time points under consideration. Error bars represent SEM. Significant differences between peak signals associated with a lapse and the average response for each state are marked with an asterisk. *$p < 0.01$, **$p < 0.001$. (Reprinted from Chee et al,[141] with permission from The Journal of Neuroscience.)

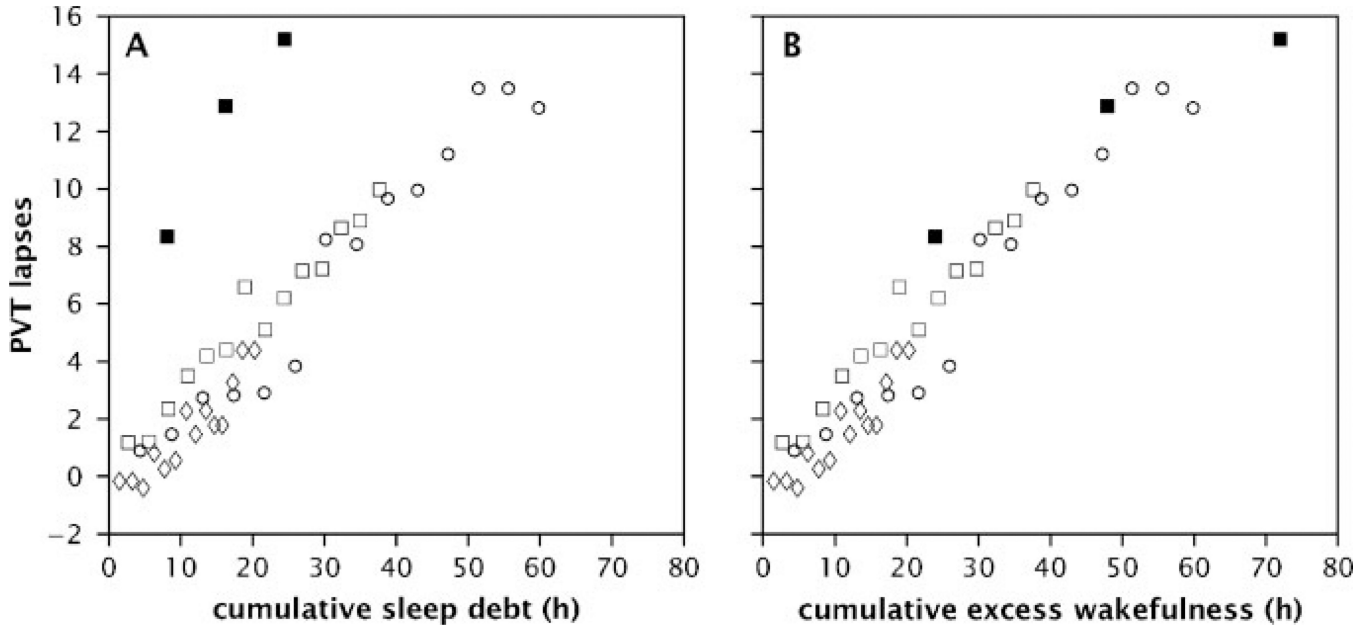

Figure 2.

A graphic comparison of performance on a behavioral alertness test following 14 days of partial sleep restriction or 3 days of total sleep deprivation, as a function of cumulative sleep debt (panel A) or cumulative excess wakefulness (panel B). Alertness was measured by lapses on the Psychomotor Vigilance Test (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 partial sleep restriction groups (8 hours = diamond, 6 hours = square, and 4 hours = open circle) and one total sleep deprivation group (at days 1, 2, and 3 of total sleep deprivation = solid square) are shown. Panel A illustrates a difference (nonlinear relationship) between behavioral performance in the partial sleep restriction and total sleep deprivation groups as a function of cumulative sleep debt. Panel B demonstrates a similarity (linear relationship) between behavioral performance in the partial sleep restriction and total sleep deprivation groups as a function of cumulative excess wakefulness. The difference in analysis between panel A and panel B affects only the total sleep deprivation condition because 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 with permission from Van Dongen et al.[68])

Table 1

Summary of Cognitive Performance Effects of Sleep Deprivation

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