The Functions of Sleep and the Effects of Sleep Deprivation

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INTRODUCTION

As humans, we spend approximately one third of our lives sleeping. Sleep is not only critical for physiological homeostasis and recovery also several essential metabolic, psychological, cognitive and immune functions. Sleep deprivation is a relative concept because it compares actual with ideal sleep duration, which is not universally agreed upon, and may vary from person to person. Expert consensus from the American Academy of
Sleep Medicine has recently estimated that a minimum of 7 h of sleep is needed on average to support optimal health in adults. The National Sleep Foundation has also published sleep duration recommendations for each age group. According to these recommendations, adults require 7–9 h of sleep, whereas teenagers require 8–10 h, and children ages 6–13 require 9–11 h. Although 7 h may be sufficient for most adults, it may not be sufficient for other age groups, especially younger populations. Despite these recommendations, a recent report from the Centers for Disease Control and Prevention estimates that over one third of the US population sleeps less than 7 h. Unfortunately, sleep is generally perceived by our society as a nonproductive state. This creates a double-bind situation in which the individual often opts to increase wake time over sleep, which paradoxically leads to reduced performance. Although many studies have demonstrated the adverse consequences of insufficient sleep, many individuals remain strikingly unaware of them.

To understand sleep deprivation, it is necessary to first measure actual sleep duration. This can be accomplished in several ways. One simple method is to have the patient keep a sleep diary (Fig. 3.1), though this method involves some level of subjective interpretation and

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**TWO WEEK SLEEP DIARY**

![An example of a 2-week sleep diary (American Academy of Sleep Medicine).](image-url)
recall, which may be impaired if the patient is sleep deprived. Actigraphy provides a more objective measurement by using an accelerometer to measure body movement (Fig. 3.2), and thus estimates sleep time and sleep efficiency. In clinical practice, however, measuring precise sleep duration is not always necessary, and self-reported sleep duration is often sufficient. Exceptions do exist, including patients with sleep-state misperception, shift workers, and professional drivers who may have a motive for misreporting.

**SLEEP AND STRESS**

Wakefulness is a state of high metabolic demand, due to the frequent need to adapt and respond to sensory inputs. In contrast, sleep is a state of energy conservation and recovery that contributes to the homeostasis of many physiological and psychological functions. This net economy in energy expenditure is more pronounced in nonrapid eye movement (NREM) sleep, as demonstrated by decreased cortical (prefrontal cortex, anterior cingulate cortex, precuneus) and subcortical (thalamus, basal ganglia, and basal forebrain) glucose metabolism in regions that are usually hypermetabolic. This reduced metabolic state reaches its lowest point in slow wave sleep (SWS), showing a 40% global decrement.

Sleep deprivation, in turn, results in hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, as evidenced by the fact that adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH) and glucocorticoid levels all increase after sleep deprivation. Sleep restriction to 4 h for 6 consecutive nights in young men results in increased levels of cortisol in the afternoon and early evening, as well as impaired glucose tolerance, a response similar to the response seen in those with noninsulin dependent diabetes.

Stress and the metabolic consequences of sleep deprivation may increase glucocorticoid secretion, and it is often difficult to separate the two. This distinction is complicated by the fact that the sleep restriction of research protocols and in vivo ecological situations that can lead to sleep loss may both constitute a stress. Furthermore, insufficient sleep and stress have reciprocal consequences, which may explain why chronic short sleepers have higher levels of cortisol when compared to chronic long sleepers. There is some data to suggest that this bidirectional relationship may be regulated by hypocretin/orexin, and hypocretinergic projections are found in a broad network responsive to CRH, including the locus coeruleus, paraventricular nucleus of the hypothalamus, bed nucleus of the stria terminalis, and central amygdala.
REGULATION OF APPETITE

With the exception of rapid eye movement (REM) sleep, which represents a relative hypermetabolic state, sleep is a period of fasting and energy conservation. Leptin is a hormone that reflects the physiological state of satiety released by adipocytes in response to food intake, while ghrelin is an appetite stimulant hormone. Sleep restriction results in decreased leptin and increased ghrelin serum levels, both of which result in increased food intake, with a predilection for energy-rich foods with high carbohydrate content.

Chronic disruption of regular sleep patterns in shift workers is associated with higher body mass indices (BMI), perhaps due to the combined impairment of the HPA axis and appetite stimulation. A metaanalysis across all age groups demonstrated an inverse relationship between hours of sleep and BMI, with each hour of sleep reduction corresponding to a 0.35 kg/m² increase in BMI.

Increased levels of TNF-α have been associated with insulin resistance, linking sleep loss, insulin resistance and weight gain. Vgontzas et al. showed increased TNF-α levels after 1 week of mild sleep deprivation in male participants. Adiponectin has anti TNF-α properties and, similar to leptin, enhances insulin sensitivity. In addition, shorter sleep duration is associated with decreased levels of adiponectine.

GH, PRL, TSH, GnRH, AND TESTOSTERONE

The growth hormone (GH) axis is closely linked to SWS. GH plasma levels peak within minutes during each SWS period and remain significantly elevated during SWS throughout the night. Furthermore, pharmacological increases in SWS with ritanserin or gamma-hydroxybutyric acid (GHB) are associated with an increase in GH plasma levels. Prolactin (PRL) secretion is subject to inhibitory dopaminergic tone, which is higher during wakefulness. Shortly after sleep onset, PRL levels increase and reach a twofold elevation during sleep, as compared to trough levels during wakefulness. Sleep exerts an inhibitory effect on thyroid-stimulating hormone (TSH) secretion, however, TSH secretion is more closely linked to the circadian rhythm than to sleep. TSH peaks in the evening and early night and reaches its trough in the afternoon. Nocturnal elevation of testosterone levels is temporally linked to the latency of the first REM period and is also observed during daytime naps. Conversely, experimental fragmentation of sleep, particularly REM sleep, leads to decreased testosterone secretion. In women, sleep has been associated with inhibition of the pulsatile gonadotropin-releasing hormone (GnRH) release in early follicular and early luteal phases.

MOOD, EMOTIONAL STABILITY AND REWARD CIRCUITS

Sleep serves an important role in mood and emotional homeostasis. Although total acute sleep deprivation has shown to have a transient but robust antidepressive effect, likely via elevation of brain-derived neurotrophic factor BDNF and serotonin, taurine and tryptophan levels, prolonged sleep deprivation in turn has deleterious effects on depression and mood stability. Subjective perception of mood and severity of unipolar depression are significantly affected by even minimal misalignment between circadian and sleep–wake cycle.
Sleep is also involved in the processing and modulation of emotional stimuli. One experiment required two groups of participants to rate the same set of photographs showing facial expressions of positive (happiness) and negative (fear, sadness, anger) emotions during two sessions, 5 h apart, with or without an intervening nap. In participants who napped, results showed lower ratings of negative fear and anger, and higher ratings of happiness between sessions. In addition, only those individuals who achieved REM sleep during their nap displayed this modulation of affective reactivity. A study recorded skin conductance response (sweating) and corrugator supercilii muscle tone via electromyography (frowning reaction) to measure unconscious reactivity to negative emotional pictures. Results showed decreased responses (habituation) when retested 2.5 h later in the group allowed to nap, compared to the group requested to stay awake.

Function MRI (fMRI) studies have demonstrated that the neurophysiological correlates of sleep-dependent emotional brain homeostasis may involve enhanced activity in the ventromedial PFC, coupled with decreased amygdala activation. Reciprocally, sleep deprivation is associated with heightened amygdala activation in response to negative stimuli and exaggerated appreciation of pleasure-evoking stimuli, correlating with increased activity in reward, and emotion-related circuits. Both findings are associated with decreased coupling on fMRI in medial and orbitofrontal cortices, areas known to be involved in behavioral inhibitory control and appreciation of rewarding experiences. Sleep deprivation generally elevates expectations of higher reward on gambling task, as nucleus accumbens activation increased with risky choices, and it attenuates neural responses to losses in the insular and orbitofrontal cortices. Taken together, these findings may explain how sleep-deprived individuals show higher risk-taking in reward-related situations with decreased insight into their negative consequences.

EMOTIONAL MATURATION

Smiles during sleep in neonates consistently emerge before smiles during wakefulness, usually observed around 2 months of age. These spontaneous “Duchenne smiles” and other emotional expressions are associated with the active sleep of neonates, the equivalent of adult REM sleep, and can be seen as early as 13th week of gestation. These facial expressions of emotions during sleep have been hypothesized to foster complex motor programs, thereby facilitating the development of the emotional and social smile.

DREAMING

Although dream activity and REM sleep have been closely associated, dreams occur in all stages of sleep, as evidenced by persistent reports of dreams after reduction or suppression of REM sleep. The quality of dreams, however, differs between REM and NREM sleep. Dreams arising from NREM sleep are usually less emotionally charged, less vivid, and less complex when compared to dreams associated with REM sleep. With the exception of frightening images often reported in NREM parasomnias, NREM mentations usually consist of images, events or situations of low emotional valence and do not have the narrative complexity of dreams arising from REM sleep.
In each civilization, symbols and meanings have been associated with dream contents and have given rise to a wide body of explanatory models, from animistic, spiritual, and religious belief systems to psychoanalytical and neurocognitive theories. In the early 20th century, Sigmund Freud and Carl Jung put forth two psychoanalytical frameworks that have since become major theories of dreaming in our modern society. While Freud hypothesized that dreams are a window into our individual unconscious psyche, Jung emphasized their relation with universal archetypes that transcend individuals, culture, and beliefs. An alternative explanatory theory suggests that experiences in dreams could provide an offline environment for simulating situations similar to the real perceptual world. According to the threat simulation theory, dreams often contain challenging and novel situations (e.g., missing an important appointment, arriving late or forgetting to study for an exam, losing money or valuables, etc.) whose purpose might be to rehearse and improve our responses in similar waking conditions. This could explain the abundance of fear-related experiences in dreams, in some respect comparable to exposure therapy.

Integrating neuroimaging, neurophysiological, and clinical evidence, the reward activation model proposed by Perogamvros and Schwartz places the mesolimbic dopaminergic pathway at the center of a circuit involved in: (1) the generation of REM via activation of the sublaterodorsal nucleus of the pons; (2) dream contents; and (3) the offline activation and consolidation of memories of high emotional or motivational values. Sex is a prominent theme in human dreams. The prominent activity of the dopaminergic reward circuits in REM sleep described previously provides a neurophysiological explanation of the universality of sex-related dreams. On a psychodynamic level, Freud viewed our dreams as a free expression of unconscious wishes. On a neurophysiological level, sexual mentation in REM sleep may be facilitated by the specific dynamics of testosterone secretion during sleep. As described previously, hormonal levels are coupled with the first nocturnal REM period, sustained during sleep, and also promoted during daytime naps. Beyond the interconnection between sexual dreams and testosterone levels, sleep has a potent effect on the activity of the neuroendocrine reproductive system and is ultimately implicated in multiple aspects of sexual satisfaction.

REGULATION OF PAIN

Sleep may also be involved in the regulation of pain via involvement of the anterior cingulate cortex and limbic pathways, which are highly connected with the emotional neural network. Four studies have shown that sleep duration below 6 h is associated with increased subjective and objective measures of pain.

COGNITIVE PERFORMANCE AND THE EFFECTS OF SLEEP DEPRIVATION

A large body of neuropsychological literature has applied the paradigm of sleep deprivation to evaluate the neurocognitive functions of sleep. These studies have some limitations, namely that sleep deprivation itself can result in a stress response with multiple metabolic, neuroendocrine, behavioral and cognitive consequences. It is also difficult to delineate
single-function deficits due to the fact that sleep deprivation affects multiple cognitive domains and behavioral aspects such as mood and affect, which determine the level of engagement for a given task. Other potential confounding factors are intersubject variability (heterogeneity of susceptibility to sleep loss between individuals) and intrasubject variability (improvement of performance on a task can reflect learning effect).\textsuperscript{55}

The psychomotor vigilance task (PVT) measures speed of responses to visual stimuli via a thumb-operated device and is not subject to learning effect. In the PVT, sleepiness manifests as microsleep or instability of the wake state. These translate to lapses of response (error of omission) or erroneous responses (error of commission), especially when the person requires significant effort in staying awake.\textsuperscript{56} In other words, this represents a balance between the homeostatic drive to fall asleep and a resistance from wake-promoting mechanisms.\textsuperscript{57} Regardless of the task, sleep deprivation generally results in a progressive degradation of the performance during extended tasks (fatigue effect) exacerbated by sleep loss.\textsuperscript{58,59} While tasks involving higher cognitive functions have been relatively less sensitive to sleep loss, possibly due to a higher level of engagement and compensatory effort,\textsuperscript{40} a large body of literature describes the consequences of sleep deprivation on sustained attention and other executive functions, procedural and episodic memory formation, and consolidation, as well as insight and creativity.

In an experiment studying reaction time over 7 days of variable degrees of sleep restriction, sleep deprivation was shown to correlate with longer reaction time on PVT testing. Longer reaction times were noted after only one night of sleep restriction (2 h of sleep reduction) compared to volunteers sleeping on average 8.5 h.\textsuperscript{60} Performance continued to diminish with each subsequent day and was directly correlated with the degree of sleep restriction. In the groups allowed to sleep for a maximum of 7 and 5 h, vigilance deficit stabilized after 5 nights, whereas in participants sleeping 3 h or less, vigilance continued to deteriorate in a linear fashion showing a twofold decrease compared to the control group at the end of the sleep restriction phase. After three nights with 8 h spent in bed, none of the sleep restriction groups returned to their baseline reaction times, suggesting that recovery from even mild sleep deprivation may last several days. This experiment also suggests that there may be an adaptive mechanism to mild and moderate chronic sleep deprivation (7 and 5 h groups) that may be insufficient to maintain performance levels in situations of severe chronic sleep deprivation (3 h group). Other studies have confirmed the finding that impairment in PVT testing increases in proportion to the degree of sleep deprivation (Fig. 3.3).\textsuperscript{61}

Sleep deprivation is known to decrease insight into one’s own performance,\textsuperscript{40,62} and some studies suggest that in conditions of total sleep deprivation, wake promoting agents could be associated with decreased self-monitoring,\textsuperscript{63} possibly due to lack of compensatory effort when compared to placebo.\textsuperscript{64} However, some evidence suggests that subjective sleepiness does not correlate well with the magnitude of cognitive impairment. In an experiment conducted by Van Dongen et al.,\textsuperscript{61} PVT, working memory, cognitive throughput measured by the digit symbol substitution task\textsuperscript{65} and serial addition/subtraction tasks (SAST),\textsuperscript{66} demonstrated a comparable degree of impairment in conditions of acute total and mild chronic sleep deprivation (sleep restriction to 6 h over 14 days), supporting the concept of a “cumulative sleep debt” with regard to executive functions.\textsuperscript{61} After 14 days, although cognitive performance reached their lowest levels, participants in the 4 h and 6 h groups reported feeling only slightly sleepy on the Stanford sleepiness scale, suggesting that individuals subjected to
chronic sleep deprivation could not reliably predict the degree of cognitive impairment on sleepiness alone. Based on the neurocognitive performances gathered across groups for the duration of the experiment, the authors estimated that the minimal 24 h requirement to attain a stable cognitive equilibrium is 3.8 h of continuous sleep. Below this critical threshold, the model diverges from a stable equilibrium and performance continues to degrade as seen in acute total sleep deprivation. This study demonstrates how relative resilience to sleepiness and stabilization of cognitive performance at a shifted new baseline may provide a false sense of coping with sleep deprivation.

Recently, functional neuroimaging techniques, including fMRI and positron emission tomography (PET), have been utilized to better understand the localization of cognitive dysfunction in cases of acute sleep deprivation. Those studies investigate either increase or decrease of blood oxygen level dependent (BOLD) measurements in fMRI or oxygen/glucose consumption in PET. The prefrontal cortex has been reported to be extremely vulnerable, showing decreased function in acute sleep deprivation. fMRI studies have demonstrated reduced activity in the prefrontal cortex after sleep deprivation in a serial subtraction task. However, in a verbal learning task, the prefrontal cortex and parietal cortex were more activated after acute sleep deprivation. Interestingly, activation of the prefrontal cortex was positively correlated with the degree of subjective sleepiness, whereas activation in the parietal cortex was positively associated with the preservation of near-normal verbal learning. These patterns of increase and decrease in cerebral activation most likely represent compensatory adaptations (CA). In CA, more activation in the prefrontal cortex with acute sleep deprivation indicates a compensation process in response to the increased homeostatic drive for sleep. The prefrontal cortex is involved in working memory, attention and executive function, functions known to be vulnerable to sleep deprivation. On the other hand, activation of the parietal lobe with sleep deprivation indicates an adaptive process to support the decreased function of other areas of the cortex. These patterns of CA have task-specific differences and indicate that sleep deprivation can result in a combination of dysfunction and compensatory hyperfunction in the brain.

Level of difficulty modulate the cerebral response, and interindividual differences can contribute to the difficulty of using neuroimaging studies as a generalized parameter of sleepiness.
It has been demonstrated in fMRI studies that activation of the frontoparietal region was more robust in participants found to be less vulnerable to the effects of sleep deprivation. This suggests that more activated CA may correlate with less vulnerability to sleep deprivation.

As mentioned, several aspects of executive function are affected by sleep deprivation. Sleep deprivation results in difficulty determining the scope of a problem in cases of distracting information and impairs divergent thinking and originality as measured on the Torrance Tests of Creative Thinking. It also affects temporal memory, as shown by lower performance on tasks of recency (inability to recall the timing for recent events), even in conditions of preserved alertness with use of caffeine. In a working memory task under sleep deprivation, fMRI studies demonstrated decreased activation in the parietal region, and increased activation in prefrontal and thalamic regions in more complex tasks. This is another example of CA.

Another function of sleep is to preserve flexible decision-making. Experiments show that acute and chronic sleep deprivation results in more rigid thinking and perseverative errors with poor appreciation of an updated situation despite intact critical reasoning, loss of focus to relevant cues, and increased risk taking, possibly due to reduced functioning of the ventro-medial PFC.

**ACCIDENTS AND SAFETY IN ACUTE AND CHRONIC SLEEP DEPRIVATION**

Performance in lane variability of driving, or accuracy and reaction time after more than 16 h of sleep deprivation, has been reported to be similar to the performance in those with a blood alcohol content of 0.05–0.1%. However, when comparing factors of sleep deprivation and alcohol intoxication, subjects who were sleep deprived showed progressive deterioration through driving, whereas subjects who were intoxicated demonstrated stable impairment throughout the entire exercise. It has also been demonstrated that the circadian rhythm affects driving performance and risk of motor vehicle accidents. Connor et al. reported a fivefold higher incidence of motor vehicle accidents between 2 and 5 a.m. compared with other times of the day. Extending these findings, Lenné et al., in a report on driving performance, especially speed control, showed deterioration in the early morning (2–5 a.m.) as well as between 2 and 5 p.m., corresponding to the mid-afternoon dip. These phenomena are more prominent in low stimulus situations, such as highway and rural driving.

Sleep deprivation has been a major issue in the medical field. One of the most significant changes in modern medical training came about after the Libby Zion’s case, with the introduction of the duty-hour regulations that helped to decrease the risk of medical errors by sleep-deprived physicians. One study demonstrated that the performance of sleep-deprived, postcall residents in vigilance, sustained attention and driving tasks is just as impaired as those with a blood alcohol concentration of 0.04–0.05%, the equivalent of 1–2 standard drinks.

**MEMORY**

The successive stages of memory are encoding, consolidation/reconsolidation and retrieval. Encoding and retrieval occur in the awake state, but adequate sleep improves all stages of memory formation, particularly consolidation and reconsolidation. Observation of improved
encoding capacity following sleep has been demonstrated in numerous studies, and accounted for by the “synaptic homeostasis” hypothesis for the brain to adapt to the widespread synaptic long-term potentiation (strengthening of postsynaptic nerve cells responses to stimulations across synapses) resulting from the incessant formation of new memories, sleep-dependent mechanisms may downscale synaptic strengths to levels that are energetically sustainable for the brain. Among all stages of sleep, slow-wave activity (SWA, 0.5–4 Hz) may contribute the most to this process.

Sleep plays an active role in memory formation because it could provide a favorable neurochemical environment with sleep-specific neurophysiological events such as SWS, sleep spindles and hippocampal ripples in NREM sleep, and hippocampal theta activity in REM sleep. According to the dual process hypothesis, NREM and REM sleep have differential involvement in declarative (episodic and semantic) and nondeclarative memory (procedural and emotional memory) consolidation, respectively.

Although reports are conflicting in older adults, SWS in young adults is positively correlated with declarative memory consolidation. Experimental enhancement of SWA via transcranial application of a 0.75 Hz oscillating potential is associated with improved declarative memory for word-pairs in young adults when compared to a sham stimulation group, indicating the specific involvement of SWA in declarative memory consolidation. Reactivation of hippocampal memory during SWS has been observed in both animal and human studies. This process involves synchronization between the hippocampus and cortex, ultimately leading to synaptic consolidation. Studies in rats demonstrate a hippocampal chronological “replay” during SWS following an experience of environment exploration (spatial learning) that are associated with hippocampal “ripples” (100–200 Hz) and sharp wave activity. In addition, coupling of hippocampal sharp-wave/ripple complexes with neocortical delta (1–4 Hz) slow oscillation patterns and spindles were demonstrated in rats during SWS. This dialog between the hippocampus and neocortex, mediated by thalamocortical sleep spindles, could facilitate transfer from the hippocampus to neocortical long-term storage sites. The specific implication of sleep spindles in memory consolidation and reconsolidation is supported by studies demonstrating a positive correlation between memory performance and spindle density, independent of the sleep stage.

REM sleep may also enhance nondeclarative (procedural, priming) memory and the emotional modulation of memory. Procedural memory involves the acquisition of motor skills. Most common experimental designs have used tasks of finger-sequence tapping, mirror tracing or other forms of visuomotor learning. Procedural memory involves a wide set of structures, including the motor cortex (supplementary motor area), basal ganglia (striatum), thalamus and cerebellum. The hippocampus is involved to a lesser extent but may be implicated in more complex motor learning tasks. While selective NREM sleep deprivation is difficult without totally depriving an individual from sleep, selective REM sleep deprivation studies have supported the view that REM sleep may be involved in the formation of procedural memory. This has been supported by the finding of decreased performance on a learned finger-sequence tapping task following REM-suppressed sleep via acetylcholine receptor blockade. On the other hand, procedural memory is not affected by REM-suppressant antidepressant medications in both depressed and nondepressed patients. In addition, several studies have demonstrated that NREM sleep events such as SWA and spindles are associated with learning of even simple motor tasks. Finally, similar to the
reactivation studies conducted with procedural memory, two studies reexposing participants to parts of a learned melody during SWS resulted in performance benefit.\textsuperscript{135,136}

Memories associated with high emotional content are also more strongly associated with REM sleep.\textsuperscript{120,121,137} Activation of limbic areas and reward circuits are observed during REM sleep and dreams, and the amygdala may be involved in regulating hippocampal memory-encoding processes.\textsuperscript{138} Memories of high emotional valence may benefit from heightened stabilization during sleep. In normal conditions, emotional memory traces may be reactivated and remodeled each night during REM sleep. This process, repeated over time, results in strengthening the nonaffective “core,” or facts of the memory and, concomitantly, weakening the affective “layer” initially associated with it.\textsuperscript{139} This model, condensed by Walker et al.\textsuperscript{139} in the formula “sleep to remember and sleep to forget,” is supported by neuroimaging evidence of decreased amygdala activity during the repeated viewing of emotional pictures after an interval filled with sleep.\textsuperscript{35} NREM sleep may also play a role in the consolidation of emotional memory as pharmacological augmentation of sleep spindles with GHB or zolpidem may improve recall of highly arousing and negative stimuli.\textsuperscript{140} Further evidence stems from the observation of odor-induced reactivation of fear memories in NREM sleep both in animals\textsuperscript{141} and humans.\textsuperscript{142} Despite this, there is lack of general agreement that NREM sleep, including sleep spindles, may be implicated in both declarative and nondeclarative memory, and REM sleep may be more specifically associated with emotional memory.

**INSIGHT AND CREATIVITY, GIST MEMORY**

Processes occurring during sleep can extract meaning and result in new insight, as suggested by historical anecdotes such as the discovery of the chemical structure of benzene or the periodic table of elements, which were reportedly sleep-induced breakthroughs.\textsuperscript{143} Some have hypothesized that memory consolidation during sleep could facilitate access to general rules or shortcuts, potentially leading to the solution of problems encountered during the wake state. Wagner et al.\textsuperscript{144} reported that 3 times more participants accessed a hidden rule for a number reduction task after sleep.

Some mechanisms during memory consolidation may also promote its integration into a metalevel of cognition. This is illustrated by experiments showing that participants tend to create “false” memories of gist words that are not present on a word list task prior to sleep, but which pertain to the list of associated words (e.g., for white coat, stethoscope, hospital, nurse, thermometer, the gist word might be doctor).\textsuperscript{145,146} In addition, REM sleep may have a lasting effect on the ability to solve complex anagrams, as demonstrated by a 32% advantage on this task in participants awakened from REM sleep.\textsuperscript{147} This effect could be related to the prolongation of a REM-related “hyperassociative state,” a state promoting novel thinking and creative problem-solving skills. Conversely, the use of creative thinking has been associated with increased REM sleep during the following sleep period.\textsuperscript{148}

**IMMUNE FUNCTION**

Sleep and circadian rhythm have a notable influence on the regulation of the immune system. Differentiated immune cells with immediate effector functions (natural killer cells and cytotoxic T lymphocytes) peak during the wake period, while naive and central memory T cells,
involved in the slowly evolving adaptive immune response, peak during sleep.\textsuperscript{149} SWS-related GH and prolactin (PRL) secretion and decreased antiinflammatory catecholamine, and cortisol levels provide a favorable endocrine milieu for antigen presenting T cell interactions, with a shift toward T helper cell (Th) 1 cytokines, increase in Th cell proliferation, and migration of naive T cells to lymph nodes.\textsuperscript{149} Sleep restriction to 4 h results in increased plasma levels of interleukin 6 (IL-6)\textsuperscript{150} and C-reactive protein (CRP)\textsuperscript{151} within 10 days, and even mild sleep restriction to 6 h over 8 days leads to elevated levels of inflammatory cytokines.\textsuperscript{18} Elevations have been shown to be mild but consistent, resulting in a state of low-grade systemic inflammation within ranges increasing cardiovascular risk.\textsuperscript{152,153} Chronic sleep loss results in an increased risk of viral upper respiratory infections\textsuperscript{154} and a higher rate of infections in shift workers.\textsuperscript{155} Reports of decreased immune response to influenza virus vaccination in individuals suffering from chronic sleep loss\textsuperscript{156} further supports the view that, although associated with elevated markers of inflammation, sleep loss results in a functional state of immunodeficiency.

There is little and conflicting data regarding quantity of sleep and cancer risk, and no evidence of an association with neurological tumors. Kakizaki et al.\textsuperscript{157} found an increased risk of breast cancer (hazard ratio = 1.62) associated with 6 h (compared to 7 h) of sleep; however, several large prospective cohort and case-control studies have failed to replicate this association. One prospective cohort study found sleep of less than 7 h to be associated with reduced ovarian cancer risk.\textsuperscript{158} Less than 6 h of sleep may be associated with colorectal adenoma,\textsuperscript{159} and both extreme short (\(\leq 5\) h) and long (\(\geq 9\) h) sleep durations may be associated with increased risk of colorectal cancer.\textsuperscript{160}

**CONCLUSIONS**

In addition to its critical function in endocrine, metabolic, and immune regulation, sleep appears to play an active and important role in maintaining health, emotional well-being and neurocognitive performance during wakefulness. Lifestyle changes have been emphasized in recent years to prevent a wide range of diseases and promote health in general. We hope that in the future a similar effort will be made to stress the importance of sleep-related lifestyle changes that can improve both sleep quality and sleep quantity, not only for our patients but also for society at large.

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