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Sleep organization and regulation

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Abstract

Article abstract: Sleep is a vital, complex state with as yet unknown functions. It is active and highly organized and is regulated by homeostatic, circadian, and ultradian processes. It consists of two distinct sleep states, rapid eye movement (REM) and non-rapid eye movement (NREM), both of which have a dramatic impact on many aspects of physiology and behavior. The significance and consequences of the REM–NREM organization of sleep are not known. On the other hand, the sleep state and its organization are quite fragile and dynamic. Any number of factors can disrupt sleep and its expression, and its nature changes over the life span. What is certain is that any reduction and/or disruption of sleep hinders an organism's ability to navigate through the waking state.

Sleep is an instinctive, appetitive behavior. Organisms sleep incessantly in utero and immediately after birth. Neonates sleep two to three times the daily sleep duration of adults. This high neonatal sleep duration during the intense postnatal period of growth is consistent with the appetitive nature of sleep. The compelling *need to sleep* (i.e., its appetitive nature) is further evident when the inability to maintain continuous wakefulness for more than 2 to 3 days is contrasted with the ability to starve oneself to death. There is something very fundamental to sleep function that has yet to be discovered. However, the past 40 years of sleep research clearly indicate what sleep is not—simply a resting brain—as popular notions and behavioral observations might suggest.

Sleep is a state characterized by stereotypic posture, minimal movement, reduced responsivity to stimuli, reversibility, and species-specific diurnal timing and duration. 1 Humans sleep in a recumbent position with eyes closed, but some mammals sleep with eyes open (e.g., cattle), some while standing (e.g., horse, elephant), and some birds while hanging by their feet (e.g., hanging parrots). The immobility of the sleep state is relative. Some fish swim in place, mammals move periodically during sleep, and walking and talking occur in some human sleep disorders. Responsivity to endogenous and exogenous stimuli is reduced but not absent. The state is also reversible. These two characteristics clearly distinguish sleep from death, coma, and hibernation. The typical total daily sleep time varies tenfold among species, from approximately 2 hours in the giraffe to 20 hours in the little brown bat. It is usually 8 hours for humans. Sleep is timed to occur predominantly in the dark hours for humans and many other mammals, but for other mammals it is linked to the light period (e.g., rodents).

Sleep scientists measure sleep electrophysiologically, which is more precise and less obtrusive than behavioral assessment would require (e.g., testing arousal threshold). Although electrophysiologic measures correlate well with behavioral observations of sleep, they also reveal further subtleties of sleep that are not apparent behaviorally or experienced subjectively. These measures indicate that sleep is an active, complex, and highly organized process consisting of two distinct brain states that have a profound impact on other physiologic functions. The simultaneous and continuous recording of the electroencephalogram (EEG), the electro-oculogram (EOG), and the electromyogram (EMG) are the accepted standard measures of sleep and waking and the two sleep states: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. 2 The nature of these two sleep states is quite distinct.

Nature of sleep.

NREM versus REM. The cortical EEG of NREM sleep is characterized by slowed frequency and increased voltage, in contrast to the low voltage (10 to 30 μ V) and rapid frequency (16 to 25 Hz) of activated wakefulness. Relaxed wakefulness with eyes closed shows an [alpha] 8 to 12-Hz EEG pattern of 20 to 40 μ V, which also slows and decreases during drowsy sleep. When arousal threshold is highest, the EEG of NREM sleep has 0.5- to 2-Hz waves of 75 μ V and greater, often termed "slow-wave" sleep. EOG tracings show rapid eye movements during wakefulness, which become slow rolling movements on the transition to NREM sleep and are finally quiescent during slow-wave NREM. The EMG, high in amplitude during wakefulness, is gradually reduced in NREM sleep, although body repositioning and motor events occur during NREM.

In dramatic contrast, the cortical EEG of REM sleep reverts to the low-voltage, mixed-frequency pattern seen during drowsy sleep. The EMG is reduced to its lowest level of the night. There is paralysis of most major voluntary muscle groups through a process of postsynaptic inhibition of motor neurons in the spinal cord. The EOG displays bursts of rapid eye movements, from which this stage gets its name.

Tonic versus phasic.

REM sleep is further characterized by its tonic and phasic features. The tonic features of REM include persistent muscle atonia and desynchronized EEG. Phasic REM events are intermittent. The eye movements of REM occur in bursts, after which there are periods of eye quiescence. Coupled with the bursts of eye movements are phasic muscle twitches, typically involving peripheral muscles superimposed on the tonic atonia. This tonic and phasic distinction is further relevant to the physiologic changes of sleep described below.

Physiologic function during sleep.

Autonomic nervous system.

Autonomic nervous system function varies from waking to sleep and from REM to NREM. 3 Relative to relaxed wakefulness, parasympathetic activity increases during NREM, tonic REM, and phasic REM. Sympathetic activity remains relatively constant in waking and NREM, with a slight reduction in tonic REM. As a result, parasympathetic activity predominates. During phasic REM, sympathetic drive increases dramatically and predominates despite the increased phasic REM parasympathetic drive.

Respiratory system.

Sleep alters breathing pattern and control. 4 During NREM sleep, there is a 13 to 15% decrease in minute ventilation as a result of two factors. First, the tonic, cortical, nonmetabolic drive to breathing that is present during wakefulness is removed with the onset of NREM sleep. Second, the reduction in skeletal muscle tone that occurs during sleep leads to a reduction of upper airway dilator muscle tone and consequently to a greater airflow resistance. During the atonia of REM sleep, airway resistance is further increased, ultimately to twice that of waking. This causes irregular breathing patterns in REM, and the irregularity is greatest in phasic REM.

The metabolic control of breathing is also altered during sleep. Hypoxic ventilatory drive is reduced in NREM sleep and declines further in REM. The hypercapnic ventilatory response is also reduced in NREM and is virtually absent in REM. Breathing during NREM sleep appears to be controlled primarily by arterial levels of CO_2, and at levels below the CO_2 threshold, breathing effort ceases. With the changed CO_2 set-point in NREM sleep relative to waking, breathing often becomes periodic at transitions between wakefulness and sleep. Thus, in elderly individuals, who often have fragmented, discontinuous sleep (e.g., frequent wake–sleep transitions), central apnea is produced. Finally, given the virtual absence of hypercapnic drive in REM, obstructive apnea in patients is prolonged.

Body temperature control.

Thermoregulation is also altered during sleep. 5 During NREM sleep, there is a lower set-point and temperature is maintained at a lower level than in waking. Sweating and shivering occur at lower temperatures during NREM sleep than during wakefulness. During REM sleep there is *no* temperature regulation, and sweating and shivering cease. If REM sleep were to persist without temperature regulation, body temperature would equilibrate to the ambient temperature. However, REM episodes typically last for 30 minutes or less, and dramatic changes in body temperature do not occur.

Regulation of sleep and waking.

Sleep is an actively regulated and organized biologic function consisting of three hypothesized processes: a *homeostatic* process determined by the amount of prior sleep and waking; a *circadian* process that organizes alternations of sleep and waking over the 24 hours of the day; and an *ultradian* process within sleep that controls the alternation between the two sleep states, NREM and REM sleep. 6 The homeostatic and circadian processes are considered independent, although interacting, whereas data suggest that REM and NREM sleep are interdependent. Although not well known, the neurobiology of the circadian process has been better described than that of the other two processes or of the interaction of the three.

The presence of homeostatic control of sleep is inferred from measurement of sleep latency at night, during the day, and from EEG slow-wave activity during sleep. The prior amount of sleep and waking is directly related to the degree of daytime sleepiness. 7 Linear reduction of the previous night's sleep time of 2 to 8 hours increases the speed of falling asleep throughout the following day on a standardized measure of daytime sleepiness, the Multiple Sleep Latency Test (MSLT). Nightly reductions of sleep time by as little as 1 to 2 hours accumulate over successive nights, reducing MSLT sleep latency. Conversely, increased nocturnal sleep time results in increased sleep latencies on the MSLT. Thus, reductions or increases of sleep time systematically alter homeostatic sleep drive. The other indicator of sleep homeostatic balance is EEG slow-wave activity. Quantification by computer of slow-wave activity during sleep has repeatedly shown a predominance of slow-wave activity during the first hours of the sleep period and declining amounts toward the last hours. During the day, after increasing durations of waking, slow-wave activity reappears during naps. 6 Total and partial sleep deprivation produce increased slow-wave activity during recovery sleep. Prevention of slow-wave activity with acoustic stimuli during the first 3 hours of sleep, without increasing waking time, results in increased slow-wave activity during the last hours of sleep. The output of these systems suggests a very precise homeostatic regulation of sleep, although the neurobiology of the system is not known.

Independent of the homeostatic process is a circadian process that organizes sleep and waking in phase with the light–dark cycle. 8 The light–dark cycle through the retinohypothalamic tract exerts a direct synchronizing effect on the suprachiasmatic nucleus (SCN), considered to be the "biological clock." The efferent projections from the SCN (or SCN-triggered hormonal signals) that convey circadian timing in regulating various physiologic rhythms are not completely understood. However, the output of this system is well characterized. 8 Circadian period, phase, and amplitude are often documented by recording body temperature, which in humans is characterized by a daily nadir in the early morning (3 to 5 AM), a peak in the early evening (5 to 8 PM), and a secondary decline over the midday (1 to 3 PM). Sleep propensity in humans, measured by speed of falling asleep or duration of sleep, parallels the temperature rhythm, with sleep propensity being greatest around the temperature nadir, least during the temperature peak, and moderate over the midday. 9 In addition, a variety of hormonal and metabolic rhythms are driven by the SCN. To name a few, cortisol, thyroid-stimulating hormone, prolactin, growth hormone, and melatonin all display a circadian rhythm. Prolactin and growth hormone are strongly linked to sleep, i.e., delayed sleep onset delays the release of these hormones. Cortisol, in contrast, displays circadian variation regardless of the timing and duration of sleep; its release begins around the temperature nadir. Melatonin release begins with the onset of darkness, and levels remain elevated until sunrise.

Finally, the ultradian rhythm is a 90- to 120-minute cycle of NREM and REM sleep. The cycle is repeated three to six times during the night. The ultradian and homeostatic processes appear to be interdependent, in that during successive NREM–REM cycles the amount of slow-wave sleep progressively declines and the amount of REM sleep increases.

Factors influencing sleep.

Age. Probably the greatest influence on sleep duration, continuity, and staging is age. The sleep of infants and children is notable, first, for its duration. 10 Neonates sleep 16 to 18 hours daily, which drops to approximately 14 hours by year 1 and to 12 hours by year 3. Secondly, during the first year of life, REM sleep occupies approximately 50% of the total sleep time. The REM sleep percentage drops to about 20% by age 3, where it remains for most of the life span. Third, slow-wave activity during NREM sleep is abundant in the preadolescent years, occupying 25 to 30% of sleep duration. Slow-wave activity begins to decline at adolescence and diminishes throughout adulthood. Daytime alertness is optimal in preadolescence, with sleep latencies at the ceiling of the MSLT (20 minutes). Peripubescence is associated with the development of daytime sleepiness, which is particularly evident during the midday.

The sleep of the elderly is characterized by the loss of almost all slow-wave activity during NREM sleep. 11 In addition, the duration of nocturnal sleep is reduced to 6 to 8 hours. These changes have suggested to some that the *need to sleep* is decreased as one ages. However, two factors argue against this interpretation. First, the elderly nap more frequently during the daytime, and on the MSLT they show greater daytime sleepiness than young and middle-aged healthy individuals. Second, the sleep continuity of the elderly is disturbed. There is an increase of brief EEG arousals that fragment sleep, either idiopathic in origin or associated with the increased frequency of two specific sleep disorders, sleep apneas and periodic leg movements. These sleep pathologies occur at increased frequency in the sleep of otherwise healthy elderly individuals. Therefore, it is concluded that the *need to sleep* is not diminished in the elderly, but rather the ability to sleep.

Sleep and daytime alertness over the middle decades are not well described. In fact, norms for the nocturnal sleep and daytime sleepiness of healthy individuals over the middle decades are not available. Table 1 presents the nocturnal sleep measurements on the first night in the laboratory and table 2 the average daily sleep latency on an MSLT conducted the following day for individuals in the fourth, fifth, and sixth decades of life. 12

***Table 1** Nocturnal sleep measures in normal middle-aged adults*[12]

	Age (yrs)		
	30–39	40–49	50–59
Sleep efficiency measures			
Sleep latency (min)	17.0 (16)	17.0 (13)	18.0 (16)
Wake in sleep (min)	28.0 (22)	30.0 (56)	57.0 (51)
Number of awakenings	6.0 (3)	6.1 (2)	6.6 (4)
Sleep time (hrs)	7.2 (0.6)	7.2 (0.6)	6.7 (1.0)
Sleep stage measures			
% Stage 1	16.0 (6)	14.0 (9)	20.0 (10)
% Stage 2	54.0 (9)	56.0 (6)	57.0 (9)
% Stages 3–4	10.0 (8)	8.0 (6)	6.0 (7)
% Stage REM	20.0 (4)	22.0 (5)	17.0 (4)
REM latency (min)	99 (45)	86 (34)	87 (40)

Data are presented as means (SD).

Table 1. Nocturnal sleep measures in normal middle-aged adults 12Data are presented as means (SD).

***Table 2** Average sleep latency (min) on the MSLT in normal middle-aged adults*[12]

	Time of day				
Age (yrs)	10 AM	12 N	2 PM	4 PM	Mean
30–39	11.5 (6.1)	10.5 (6.3)	12.5 (6.9)	11.2 (6.6)	11.5 (5.1)
40–49	12.8 (4.9)	11.8 (6.9)	11.2 (6.3)	12.8 (6.7)	12.1 (4.5)
50–59	9.5 (6.3)	8.5 (4.2)	9.2 (5.8)	12.2 (7.0)	9.2 (5.4)

Data are presented as means (SD).

MSLT = Multiple Sleep Latency Test.

Table 2. Average sleep latency (min) on the MSLT in normal middle-aged adults 12Data are presented as means (SD).MSLT = Multiple Sleep Latency Test.

None of the 12 volunteers of each age group (two-thirds male; one-third female) had any current medical illness, current or past mental illness, history of alcohol and drug abuse, or current CNS-acting drug use. All volunteers went to bed at their usual bedtimes and arose 8 hours later. Standard nocturnal polysomnograms and MSLTs were conducted.

The reduction of sleep efficiency and sleep time that is characteristic of the aging process begins to emerge as a trend during the sixth decade. Sleep maintenance (i.e., minutes of waking in sleep) rather than sleep onset is disturbed. A slight reduction of NREM slow-wave sleep (i.e., percentage of stage 3–4 sleep) from 10% in the fourth-decade group to 6% in the sixth-decade group is also shown. The average daily sleep latency on the MSLT is also reduced in the sixth-decade group.

Environmental factors.

New sleep environment.

Probably the most universal environmental influence on sleep is an unfamiliar sleep surrounding. Early in the modern era of sleep research, a "first-night" effect in the sleep laboratory was identified. 13 Compared with sleep on subsequent nights, the first night in the laboratory is characterized by increased sleep latency, increased wakefulness in sleep, greater amounts of light sleep and, typically, an increased latency to REM sleep. 14 In some cases, other aspects of the structure of sleep are altered as well; amounts of REM and slow-wave sleep are reduced. After one or two nights, these alterations in sleep disappear. As a consequence, laboratory research studies of sleep always include an adaptation period of one or two nights before baseline data are collected.

Noise.

Noise appears obvious as an influence on sleep. There is a growing literature of basic research on the effects of noise on sleep. 15,16 Briefly, the evidence shows that wide variations exist among individuals in sensitivity to sounds during sleep. 17 Furthermore, the meaning or relevance of the sound is also critical. 18 In other words, there is a basis to the commonly held belief that a mother will awaken at the softest whimper of her child but will sleep through a thunderstorm. Snoring is another example. Some bed partners are able to tolerate the most raucous snoring and snorting, whereas others find a soft wheeze extremely offensive and disruptive to their sleep. It should be recognized that sleep-disruptive noise is not necessarily remembered upon awakening in the morning. 19

Studies of the effects of noise on sleep have consistently shown disturbed sleep. 15 The numbers of body movements, awakenings, and sleep-stage shifts are increased. The amount of wakefulness and light sleep is also increased, whereas the amount of slow-wave and REM sleep may be reduced. Recent interest has focused on the brief-arousal 3- to 15-second episodes of EEG speeding or [alpha], which are not sufficient to result in wakefulness by sleep staging standards or behavioral criteria. 19 The arousals are associated with increased daytime sleepiness as measured by the MSLT. Although adaptation to the disruptive effects of noise on sleep appears to occur quite rapidly, it is not complete. Cortical EEG arousal responses are reduced but cardiovascular reactivity remains. 15,19

Temperature.

Temperature is another of those obvious factors that is difficult to evaluate but important to the quality of sleep. Patients often consider inadequate temperature regulation to be the cause of a transient sleep complaint. As with noise, there are marked individual differences in sensitivity to temperature variations and in optimal sleeping temperature. Transient deviations from optimal temperature clearly do disrupt sleep. Systematic laboratory studies generally show that persons sleeping at temperatures above and below thermoneutrality exhibit disturbed sleep. Interestingly, the disturbance usually is not in the ease of falling asleep but rather in the ability to maintain sleep. 20 The amounts of wakefulness and light sleep are increased and the amount of REM sleep is decreased. The sleep pattern changes associated with cold and heat are similar, although cold produces more extreme changes in pattern than does heat. 20

Sleep surface.

The adequacy of the individual's sleep surface is the source of a surprising number of insomnia complaints. In a survey of the United States public concerning the quality of sleep, conducted by the Gallup Organization, 7% of respondents indicated that their sleeping problems were related to an uncomfortable mattress. 21 However, the few objective studies of sleep surfaces have failed to demonstrate differences in sleep due to sleep surface. In normal individuals, waterbeds had no demonstrable effect on sleep after a 2-week adaptation. 22 Presumably, a change in sleep surface may have a beneficial effect in specific patient populations (e.g., arthritic patients), but there are no studies demonstrating the possible beneficial effects of sleep surface.

Sleep position.

Sleep position also affects the quality of sleep. The usual human sleep posture is horizontal. There are circumstances in which it becomes necessary to sleep with the back angled from the horizontal (e.g., sleeping in car or airplane seats). Polysomnographic study of the sleep of healthy individuals in chairs with back angles of 40°, 53°, and 72° from the horizontal have shown increased wakefulness during the sleep period and reduced total sleep time compared with sleep in a bed. 23 The extent to which individuals can adapt to unusual sleep postures is not known. There are those who, for various health reasons, do habitually assume unusual sleep positions, but how the sleep of such persons might be compromised is not known.

Drug use.

Almost every drug that crosses the blood–brain barrier has an effect on sleep. The nature of the effect may be an alteration of sleep onset and/or continuity and it may be experienced immediately and/or on discontinuation of use. 24 As might be expected, stimulants, including caffeine, amphetamines, and cocaine, delay sleep onset and disrupt sleep continuity, whereas depressants, including alcohol, barbiturates, and benzodiazepine agonists, promote sleep onset and enhance sleep continuity. With regard to sleep staging, alcohol and barbiturates are reported to increase slow-wave sleep and benzodiazepines to suppress slow-wave sleep. Barbiturates, alcohol, cocaine, and amphetamines suppress REM sleep; benzodiazepine agonists do not. With repeated administration of both stimulants and depressants, tolerance to the REM-suppressing effects develops rapidly (i.e., within a week). The same is true for the opiates; although they suppress REM, tolerance develops. In contrast, the drugs with the greatest suppressant effect on REM are the antidepressants, and tolerance to their REM suppression is minimal over weeks of administration.

On discontinuation of drugs, rebound effects are observed. For example, after REM-suppressing drugs are discontinued, enhanced amounts of REM sleep are observed for 1 to 2 nights. 25 Often the REM sleep is fragmented and is disrupted by brief awakenings. REM rebound is reported after discontinuation of stimulants, depressants, and opiates. After discontinuation of some depressants, a rebound in waking occurs; in other words, sleep efficiency is reduced. After alcohol consumption, a rebound in waking occurs during the second half of the night, because the typical alcohol dose is completely metabolized during the first half of the night. 26 High doses (e.g., doses beyond the asymptote of hypnotic activity) of benzodiazepine agonists lead to rebound waking on the first night of discontinuation. 25 This phenomenon is referred to as "rebound insomnia." Stimulant discontinuation often produces rebound sleepiness, such as that observed after the discontinuation of amphetamines and cocaine. The presence and extent of rebound wakefulness or sleepiness are probably a product of the dose and duration of administration. However, studies have not systematically demonstrated that relation.

Consequences of sleep alteration.

The consequences of alterations in sleep continuity and sleep time are becoming clear, but those for sleep staging are not; the clinical significance of alterations of slow-wave sleep is not certain. Slow-wave activity is often interpreted to indicate the "depth" of sleep. If "depth" means ease of arousal, then the enhanced slow-wave sleep of children and the diminished slow-wave sleep of the elderly are consistent with that view. However, benzodiazepines suppress slow-wave sleep and elevate arousal threshold, and alcohol elevates both slow-wave activity and arousal threshold. If "depth" means absence of motor activity, then REM sleep is "deeper" than slow-wave sleep. Similarly, the consequences of REM suppression are not known. In patients with primary depression, REM suppression is temporally associated with mood elevation. In healthy individuals, the only apparent consequence of REM suppression is REM rebound.

Reduction of sleep time and sleep continuity have a clearly established impact on many aspects of daytime function. A reduction of sleep time from a given individual's daily *sleep need*, which is probably genetically determined and on average is 8 hours, leads to reduced daytime alertness. 27 The reduced alertness (or increased sleepiness) can be expressed as lapses in attention, difficulty remembering, and increased risk for automobile accidents. Both laboratory and epidemiologic studies have documented these effects. A number of subgroups in the population report reduced sleep times and increased daytime sleepiness. Young people, teenagers, and young adults report approximately 7 hours of sleep daily, and in laboratory studies they display increased daytime sleepiness on the MSLT. 7 Shift and night workers also report short sleep times, about 6 hours daily on average, and have higher rates of industrial and automobile accidents. 7

Similarly, the consequences of disrupted sleep continuity have been demonstrated. Laboratory studies in which the sleep of healthy individuals is experimentally fragmented with auditory stimuli have produced increased daytime sleepiness and reduced attention and psychomotor performance. 28 Patients whose sleep is fragmented by primary sleep disorders, such as apneas or periodic leg movements, are sleepy as measured by the MSLT. 7 Successful treatment of the primary sleep disorder restores sleep continuity and daytime alertness in these patients. The elderly comprise a subgroup of the population exhibiting fragmented sleep and increased daytime sleepiness.

Conclusions.

Sleep is vital, albeit with uncertain functions. It is an active and highly organized state that has a dramatic impact on many aspects of physiology and behavior. On the other hand, the sleep state and its organization are quite fragile and dynamic. Any number of factors can disrupt sleep, and its expression and nature change over the life span. The significance and consequences of the REM–NREM organization of sleep are not known. What is certain is that any reduction and/or disruption of sleep hinders an organism's ability to navigate through the waking state.

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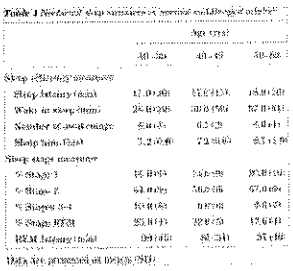

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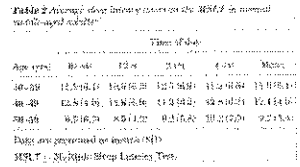

Table 2

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