



Review

The Functions of Sleep

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Abstract: Sleep is a ubiquitous component of animal life including birds and mammals. The exact function of sleep has been one of the mysteries of biology. A considerable number of theories have been put forward to explain the reason(s) for the necessity of sleep. To date, while a great deal is known about what happens when animals sleep, there is no definitive comprehensive explanation as to the reason that sleep is an inevitable part of animal functioning. It is well known that sleep is a homeostatically regulated body process, and that prolonged sleep deprivation is fatal in animals. In this paper, we present some of the theories as to the functions of sleep and provide a review of some hypotheses as to the overall physiologic function of sleep. To better understand the purpose for sleeping, we review the effects of sleep deprivation on physical, neurocognitive and psychic function. A better understanding of the purpose for sleeping will be a great advance in our understanding of the nature of the animal kingdom, including our own.

Keywords: sleep; sleep function; sleep deprivation; sleep theories; sleep restoration

Abbreviations: EEG–electroencephalogram; REM–Rapid eye movement; NREM–non rapid eye movement; BCE–Before the common Era; ICSD3–International classifications of sleep disorders third edition; SWS–slow wave sleep; Ag–Antigen; IgG–Immunoglobulin G; RNA–Ribonucleic Acid; BRFSS–Behavioral Risk Factor Surveillance System; CRP–C reactive protein; PTSD–posttraumatic stress disorder; PVT–psychomotor vigilance task; TIB–time in bed; SWA– Slow Wave Activity; h–hour(s)

1. Introduction

All mammals and birds sleep, that is they assume a state of reduced perceptual engagement from the environment with elevated arousal threshold. Sleep is a neurologically dynamic behavior with physical quiescence, elevated arousal threshold and a state of rapid reversibility. Historically, sleep was sometimes considered to be a state between wakefulness and death. In fact, it could be

argued that comparison of sleep to a deathlike state, i.e. an absence of function, may have contributed to the delay in the modern scientific study of and understanding of sleep. Sleep patterns vary among species in often surprising ways in order to meet the particular life patterns of each species. Although “we all do it,” the actual overall function of sleep is as yet incompletely understood. The great sleep researcher and pioneer Allen Rechtschaffen noted that “if sleep does not serve an absolute vital function, then it is the biggest mistake the evolutionary process ever made.” [1]. There are many biologic functions associated with sleep, including those that lead to restoration of body, brain and neurocognition. In a later publication, Rechtschaffen reviewed a number of the then existing scientific ideas as to the importance of sleep [2]. He notes that sleep is ubiquitous in higher animals. On the surface, sleep appears to be maladaptive—sleeping humans, for example, desist from procreation, self-protection, and even “making a living.” There appears to be a homeostatic regulation of sleep and sleep loss is followed by rebound sleep. It has been shown that when totally deprived of sleep, rodents die.

Further, “sleep” is not a single “state of being.” Sleep in mammals is actually organized in cycles composed of two fundamentally different “states of being:” namely Rapid Eye Movement (REM) and non-REM sleep (NREM). The latter is further subdivided into “deep” (slow wave) and “light” stages (Stages 1 and 2). These different sleep stages all have differing biologic manifestations, neurologically and physically. Specific types of brain activity distinguish them. On electroencephalogram (EEG) study, NREM sleep reveals local and global slow cortical oscillations of wave activity (stage 3) and sleep spindles (stage 2). In contrast, during REM sleep the EEG patterns of the brain bear a resemblance to those in waking with associated eye movement in phasic REM stage, and without eye movement in tonic REM sleep [3].

Circadian and homeostatic processes regulate sleep [4]. This is often referred to as the “two-process model” for determination of the state of alertness. Circadian regulation is demonstrated by the maintenance of a 24-hour rhythm cycle in sleep propensity that is independent of prior sleep. The natural cycle of the brain is slightly longer than 24 hours, but it is “resynchronized” each day by the advent of blue light. Thus, normal circadian rhythmicity assures that humans are awake in the daylight (mostly morning) and ready for sleep in the night. Secretion of the hormone melatonin at night by the pineal gland in the brain is one important mechanism assuring the function of the “biologic clock.” Homeostatic regulation is reflected by rise in sleep propensity during waking and its dissipation during sleep. The interaction between circadian driven sleepiness-alertness cycles, and homeostatic (sleep deprivation or excess of wakefulness) is what determines the state of alertness-sleepiness.

As will be reviewed in this article, sleep deprivation has many and varied adverse effects on body, mind and psyche. However, one cannot help but wonder as to why the creator (through evolution) saw fit to design animals with the necessity of a period of down time. After all, man’s mechanical contrivances do not usually need to be taken out of commission for daily servicing. For example, for an automobile, a tune-up every 3000 miles or so does quite well.

For the purposes of this review, we have taken the view that we can learn about the “function” of sleep by learning about the pathophysiological consequences of sleep deprivation. We have briefly reviewed some of the historical notions about the function of sleep, and have concentrated most of this review on what is known in the scientific literature about the effects of sleep deprivation in humans on physical, mental and psychic restoration.

2. Sleep Throughout History

Sleep was in fact well recognized by the ancients, and even revered as a state in which human consciousness was open to inputs (supernatural) to which it is not normally receptive. In Genesis 28, verses 11 ff, God describes his plans for the Hebrew Patriarch Jacob while the Patriarch was asleep:

“And he lighted upon the place, and tarried there all night, because the sun was set; and he took one of the stones of the place, and put it under his head, and lay down in that place to sleep. And he dreamed, and behold a ladder set up on the earth, and the top of it reached to heaven; and behold the angels of God ascending and descending on it. And, behold, the LORD stood beside him, and said: ‘I am the LORD, the God of Abraham thy father, and the God of Isaac. The land whereon thou liest, to thee will I give it, and to thy seed.’”

(Genesis 28, verses 11–13)

Dream interpretation was a major activity among ancient holy men, as well as modern psychotherapists. The ancient Egyptians constructed temples for the goddess Isis where congregants and priests would gather to perform dream interpretations. Note the importance of dream interpretation for the “career” of Joseph in ancient Egypt. Joseph’s knack for interpreting Pharaoh’s recurring dreams enabled Joseph’s rise to power from slave to vice regent of the ancient Egyptian kingdom.

The ancient Greeks recognized that sleep was not only a portal for divine, or sometimes demonic, interface with man, but of great physiologic importance to well-being. In approximately 350 BCE, Aristotle, in a surprising “modern” evaluation of sleep reported that:

“It is inevitable that every creature which wakes must also be capable of sleeping, since it is impossible that it should continue actualizing its powers perpetually. So, also, it is impossible for any animals to continue always sleeping.” [5]

Throughout most of man’s history human sleep was considered a “state” in which man was open to communication to deities and demons, or in which man’s “soul” could wander unfettered by the bounds of the physical body. Dreams were variously considered to be messages from seemly or unseemly supernatural entities, or, later as the study of the human mind developed, a reflection of “inner” unexpressed human desires or psychic traits.

The study of sleep as a physiologic phenomenon was addressed in the early 20th century by the French scientist Henri Pieron, in his pioneering treatise “Le problem physiologique du sommeil.” [6]. In the 1920’s Nathaniel Kleitman, the father of American sleep research, performed a series of pioneering studies on the regulation of the sleep/wakefulness cycle. His crucial work included descriptions of sleep characteristics in different populations and effects of sleep deprivation. In 1953, along with his graduate student Aserinsky, he described the state of REM sleep [7]. Another of Kleitman’s students, Dr. William C. Dement, extended Kleitman’s work, describing the cyclical nature of sleep and established that vivid dreams occurred during REM sleep. In addition, Dement engaged in research on animals that opened the way for elucidation of electrophysiological, pharmacological, and biochemical correlates of different sleep stages under various circumstances [8]. Since the pioneering work of these and many other workers, the field of sleep medicine has expanded and become a recognized medical discipline with a specified training process, research

tracts, and board exam. There are 59 recognized sleep diagnoses (International classifications of sleep disorders third edition ICSD-3) as well as additional isolated symptoms and normal variants. A large volume of excellent research has been done, and various functions and dysfunctions of normal and abnormal sleep have been identified. We now review some of the modern ideas as to the purpose of sleeping at all as well as effects of sleep deprivation on physical, neurocognitive and psychic function. Table 1 summarizes some of the current and previous scientifically grounded theories as to the overall function and purpose of sleep.

3. Role of Sleep in Physical Restoration

Multiple theories have attempted to explain the role of sleep as a period of physical restoration that serves as a time of growth and repair for the body, but much remains unknown.

Recently, Schmidt proposed a unifying theory of sleep based on the need to optimally allocate limited energy resources to essential biological processes, the Energy Allocation Model of Sleep [9]. According to this theory, the sleep-wake cycle evolved to perform unique and essential biological processes during sleep as a way to decrease the energy requirements of wakefulness and reduce total daily energy expenditure.

A major argument in favor of the restorative function of sleep is the observation that hormones released during sleep have a predominant anabolic function, such as growth hormone, as opposed to hormones associated with wakefulness, which tend to have a catabolic effect, such as cortisol, which is suppressed during sleep, [10] with the amplitude of the circadian cortisol decline dampened by sleep restriction [11].

Most growth hormone pulses occur during slow-wave sleep (SWS), with most pulses occurring shortly after sleep onset in the first phase of SWS sleep [12], with levels of growth hormone markedly diminishing during sleep deprivation [13]. The highest levels of prolactin are noted during sleep [14] and testosterone release increases during sleep in males [15].

Sleep is believed necessary to conserve energy, with lower energy expenditure noted during sleep, and sleep deprivation associated with increases in total daily energy expenditure. The lower metabolic rate of sleep may allow biological processes occurring during sleep to be completed at a lower overall energy cost compared to wake time. Jung et al. [16] evaluated seven healthy participants aged 22 ± 5 years after normal sleep, sleep deprivation and during recovery. Compared to baseline, 24 h energy expenditure was increased by 7% during sleep deprivation and decreased by 5% during recovery. During the night time, energy expenditure was increased by 32% on the sleep deprivation night and decreased by 4% during recovery sleep compared to baseline.

However, despite the above mentioned study and others, the effects of sleep restriction on energy expenditure are not completely understood. Most studies suggest that short sleep duration is a risk factor for weight gain and the development of obesity [17]. Based on the review by Klingenberg et al., although increased energy intake is the most prevailing explanation, short sleep duration does not seem to significantly affect total daily energy expenditure. Although there is limited evidence, other factors that could influence energy metabolism include up-regulation of thyroid hormones and glucocorticoids [17].

Multiple additional factors also appear to play a role, as sleep deprivation alters appetite regulation and is associated with increased hunger, appetite, and food intake. In a study of 12 normal weight healthy men, two days of sleep restriction was associated with reductions in leptin (anorexigenic hormone), elevations in ghrelin (orexigenic factor) and increased hunger and appetite [18]. Sleep restriction resulted in an increase in appetite that correlated with an increase in total cortisol

levels [11]. There is also positive energy balance—weight gain—when sleep subjects are allowed to freely access high caloric food after sleep restriction. In a controlled laboratory environment [19], after five consecutive nights of 4 hour (h) time in bed (TIB) compared to control conditions, sleep-restricted subjects gained more weight and consumed extra calories. The increased daily caloric intake was due to more meals, and the consumption of additional calories and higher percentage of calories derived from fat during late-night hours.

The immune regulatory functions of sleep are still not well understood, but recent work points to sleep acting as an adjuvant to enhance the early stage of the immune response. Lange et al. [20] compared the immune response after hepatitis A virus vaccinations in 27 healthy men who either slept or stayed awake in the night following inoculations. Sleep after vaccination doubled the frequency of antigen (Ag)-specific T helper (Th) cells, increased the fraction of Th1 cytokine-producing cells and increased Ag-specific Immunoglobulin G1 (IgG1). These effects were associated with high sleep slow-wave activity (SWA) during the post vaccination night. Other areas of the immune system, inflammation and the genes that mediate these responses may also be affected by sleep deprivation. Sleep loss affects the cellular and genomic mechanisms that contribute to inflammatory cytokine activity. After one night of sleep loss, monocyte production of interleukin 6 and tumor necrosis factor alpha in 30 healthy adults was greater than following uninterrupted sleep. In addition, sleep loss induced a more than 3-fold increase in transcription of interleukin 6 messenger ribonucleic acid (mRNA) and a 2-fold increase in tumor necrosis factor alpha messenger RNA [21].

Epidemiological studies have found that both long sleep and short sleep duration are associated with increased risks of all-cause mortality. Sleep duration shorter or longer than 7 hours is associated with a significantly elevated risk of all-cause mortality, with sleep duration of 7 hours being optimal and associated with the lowest mortality [22]. A recent study [23] explored the potential combined effect of both disturbed sleep and the quantity of sleep on cause-specific mortality in 9,098 healthy men and women followed over a mean of 22 years. In men, short sleep (≤ 6 h/night) and disturbed sleep were not independently associated with cardiovascular disease mortality, but there was an indication of higher risk among men who experienced both. In women, short sleep and disturbed sleep were independently associated with cardiovascular disease mortality. Of note, in this study, any of the sleep measures had no association with death due to cancer or other causes.

Multiple negative cardiometabolic health outcomes have also been associated with reduced sleep time in multiple studies. In an epidemiological study of 30,934 participants from the 2009 Behavioral Risk Factor Surveillance System (BRFSS), sleep duration < 5 h (versus 7 h) was related to body mass index, obesity, diabetes, hypertension, hypercholesterolemia, heart attack and stroke [24]. The mechanisms underlying the association between sleep restriction and increased cardiovascular risk are not clear. One potential mechanism may be through activation of inflammatory processes during sleep loss. C-reactive protein (CRP) and other inflammatory markers associated with cardiovascular disease risk increase in healthy adults following sleep restriction [25]. Insufficient sleep is also associated with alterations in hypothalamic-pituitary-adrenal axis [11] and the endocrine and metabolic effects of sleep restriction resemble normal ageing and, thus, may increase the severity of age-related chronic diseases [26]. Sleep deprivation is also associated with increased blood pressure, urinary excretion of norepinephrine and heart rate, which suggest an increase sympathetic nervous system activity [27]. In addition, sleep restriction has been shown to have a negative impact on carbohydrate metabolism and endocrine function, with lower glucose tolerance thyrotropin concentrations, raised evening cortisol concentrations and increased activity of the sympathetic nervous system [26].

Although understating fully the function of sleep in physical restoration remains elusive despite ongoing research, the clear adverse effect of both short term and chronic sleep restriction on function represents at least indirect evidence of the beneficial role of sleep in all of us. Adequate sleep is essential for health. Restricting sleep restriction below a person's individual optimal sleep time can cause a wide range of neurobehavioral deficits, and also adverse effects on endocrine functions, metabolic and inflammatory responses. [28]

4. Sleep is Essential for Learning and Memory

It is well documented that sleep is essential for motor skill learning. Sophisticated experimental designs such as that employed by Walker and colleagues [29] have demonstrated that even after controlling for confounding factors including the timing of motor skills training, testing and retesting, and sleep, as well as additional practice, sleep enhances motor learning. For example, accounting for all of these factors, a night of sleep resulted in a 20% increase in motor speed without loss of accuracy regardless what time of day training or sleep took place. Interestingly, the degree of improvement motor learning was associated with percentage of NREM 2 sleep late in the night [29]. Similarly, naps have been found to improve same-day motor learning, and improvements have correlated with NREM 2 sleep during the nap [30].

Similarly impressive results have been found in studies of memory formation. For example, Gais and colleagues [31] administered a paired-word association test to 8 men and 8 women and found improved results following early night sleep, high in slow waves. In a subsequent study designed to explore causal relations between SWS and memory formation, Marshall et al. [32] demonstrated that induction of slow waves enhanced retention following learning of a word pair list.

Although a detailed discussion is beyond our scope here, it is worth noting that in addition to the two studies cited above, others have postulated specific roles for sleep stages including REM, SWS, and even sleep spindles characteristic of stage NREM 2 sleep in learning and memory [33]. For example, De Koninck and colleagues [34] found that among students ($n = 10$) in an intensive language course, learning efficiency during the course was positively correlated with increases in REM sleep relative to baseline. Interestingly, experimental studies of sleep restriction have found that when time in bed is restricted, the proportions of SWS and REM are protected. That is, stage 2 NREM sleep decreases dramatically, but the proportions of SWS and REM remained relatively unchanged [28], raising the possibility that SWS and REM are necessary for higher-level cognitive functions necessary for survival. Readers are referred to other excellent reviews for further consideration of the electrophysiological, metabolic, and cellular mechanisms of sleep loss on learning and memory [35].

In light of the significant role of memory in overall affect as well as psychological disorders such as depression and posttraumatic stress disorder (PTSD), it is perhaps not surprising that alterations in sleep architecture can be considered core features of these conditions. Further, sleep loss appears to influence the negative cognition that characterizes many psychological conditions as well as exacerbate subjective distress. A study by Walker is illustrative [36]. Participants were randomized either to sleep normally at home (i.e., control), or to self-sleep deprive by maintaining wakefulness for 36 h prior to participation. Upon arrival, all participants were then given a list of words to memorize and allowed to sleep normally for two nights. At follow-up, an unexpected recognition task was administered, and participants in the sleep-deprived group recalled 40% fewer words than controls. Further, as the original list covertly included words carrying neutral, negative, or positive emotional valence, it was observed that the sleep-deprived group demonstrated poor

recall of neutral and especially positive words. However, no comparable deficit in negative word recall was observed. These results suggest not only that baseline sleep deprivation negatively impacts memory encoding and positive memory encoding in particular, but also that negative stimuli are largely resistant to the effects of sleep loss. Walker has proposed a helpful rubric to understand the role of sleep in memory formation, whereby sleep both encodes essential information to storage and also removes the emotionality from memories, thereby de-potentiating recall of adverse events over time. [37]

5. Sleep Loss Impairs Neurobehavioral and Neurocognitive Performance

In addition to the positive effects of sleep on motor learning and memory, a substantial body of literature demonstrates that the effects of sleep loss on neurocognitive performance are both striking and acute [38]. Two highly controlled experimental studies remain particularly salient to our understanding of the consequences of sleep loss in these domains. In the first of these, Belenky and colleagues [39] recruited 66 healthy commercial truck drivers to spend 14 days in their sleep laboratory. Participants were subsequently randomized to either 3, 5, 7, or 9 h in bed for 14 subsequent nights. The primary neurobehavioral performance outcome was the psychomotor vigilance task (PVT), a valid and reliable measure of accuracy and response time [40]. Relative to their baseline performances, participants in the 3 h and 5 h conditions demonstrated increasingly more misses and increasingly slower response times over 7 nights. Similarly, the response times of those randomized to 7 h (TIB) became increasingly slow as the week progressed. The accuracy and response times of participants in the 9 h condition remained relatively unchanged over the week. It is interesting to note that the accuracy of participants on the 9 h condition actually improved during the first few days of the study, suggesting the possibility that participants benefited from the increase to 9 h TIB concurrent with enrollment in the study.

In a similarly intense-to-execute study, van Dongen and colleagues [41] randomized 48 healthy adults between the ages of 21–38 years to either total sleep deprivation for 3 consecutive days or to sleep restriction of 4, 6, or 8 h TIB for 14 consecutive nights. Primary outcome measures, including both the PVT and tests of working memory, were administered every two hours throughout the study. As in the Belenky et al. [39] study, acute and cumulative deficits were observed in the shortest sleep groups, with the behavioral alertness and cognitive performance of participants in the 4 h and 6 h TIB groups eventually mirroring the neurocognitive performance of participants in the total sleep deprivation group. Interestingly, cognitive deficits in the van Dongen study were correlated with 24 hour wake time, the longer the wakefulness, the greater the deficit.

In exploring of the effects of chronic sleep loss, a third study warrants consideration. Rupp and colleagues [42] recruited 24 healthy young adults between the ages of 18–39 to explore whether prophylactic sleep banking might ameliorate the aforementioned effects of sleep loss. In this design, participants wore actigraphs and completed sleep diaries for two weeks in order to determine baseline sleep duration. Next, the in-laboratory portion of the study began, and participants were randomized to either one week of their individual baseline sleep duration or one week at 10 h TIB. All participants then completed 7 nights of sleep restriction (3 h TIB) followed by 5 recovery nights (8 h TIB). Neurocognitive performance measures including the PVT and others were administered each hour from 8:00 AM through 6:00 PM throughout the laboratory phases of the study. In both the usual and extended sleep groups, within subjects performance decreased rapidly across days of 3 h TIB. However, between groups performance was significantly less impaired in the extended sleep

group when contrasted to the usual sleep group. Impressively, between groups differences persisted even following 5 recovery nights of 8 h TIB.

In aggregate, these experimental studies suggest that among healthy adults, neurocognitive performance is impaired when the nightly sleep period is restricted to less than 7 hours. Further, the amount of sleep restriction demonstrates a dose-response to performance impairment, and within-group performance continues to worsen over time. In other words, the neurocognitive sequelae of sleep loss are both acute and cumulative. Perhaps most important, the subjective reports of participants in these studies did not correspond to their objective performance, suggesting that in spite of the obvious deficits caused by sleep loss, humans are unable to assess their own functional capacity and overestimated their ability to perform. Finally, the negative effects of sleep loss can be reduced by prophylactically extending sleep prior to the period of sleep restriction.

6. Sleep Function Theories

Since the late 20th century there have been numerous hypotheses as to the function of sleep. Some of these are summarized in Table 1. One of the earliest theories of sleep function by Meddis [43] and Webb [44,45] and later by Siegel [46] is an adaptive immobilization pattern of an animal for protection from predators. In other words, sleep has no physiological benefit apart from filling up the time. Moreover, the physiologic drive observed with sleep deprivation is a mechanism to maintain immobility during the rest phase of the circadian cycle. However, others consider increased sleep pressure after sleep deprivation as a behaviorally maladaptive process [2] since the symptoms of sleep deprivation have a number of negative consequences like increase waking predation risk.

In the mid 1990's Berger and Philips [47,48] hypothesized that the primary function of sleep was to conserve energy. This is challenged by the presence REM sleep, which is characterized by increased brain activity, metabolism and energy use. In addition, the amount of total body energy saved during sleep relative to wakefulness is relatively small and it is unlikely that the most important reason for sleeping is energy conservation. Another theory by Adam [49] and Oswald [50] was that sleep provides restitution through protein synthesis. While this may be focally important (e.g. growth hormone is released primarily during SWS), it has been shown that whole-body protein synthesis is greater during wakefulness or feeding [51]. Further, if the primary function of sleep was to synthesize proteins, then the larger the animal, the more would be the sleep requirement. In fact the contrary is true [52].

Similarly, Benington and Heller [53,54] suggested that sleep assists in replenishment of glycogen, which is a reserve energy store. However, in rodents, it has been shown that glycogen replenishment occurs during the first hour of sleep and upon awakening, the increment is lost within 2–5 minutes, suggesting that glycogen replacement cannot explain the length of sleep [55].

Reimund [56] also hypothesized that sleep has a restorative function. He postulated that sleep clears free radicals that have accumulated in the brain during wakefulness. However, this does not explain the benefits of REM sleep or sleep benefits for other organs. Recently, Lulu Xie [57] demonstrated changes in brain interstitial volume over the sleep-wake cycle and increased clearance of amyloid in during sleep in mice. This theory favors a restorative function for sleep in the brain. However, differences over different stages of sleep were not addressed.

Another wave of theories have emphasized the function of sleep at the cellular level. Morruzi [58,59] suggested that sleep facilitates slow recovery and stabilization of synapses activated during consciousness. In contrast, Krueger et al. [60] and Kavanau et al [61–64] proposed that sleep preserves synapses that are under-used and stabilizes use-dependent synapses respectively. In fact,

there are no functional studies to support synaptic enhancement, reduced transmission or stabilization of neurons. According to Jouvet's [65] hypothesis, neuronal activities occur preferentially during REM sleep through activity dependent maturation of sensory and motor circuits. However, this hypothesis deals exclusively with REM sleep and does not address functions of non-REM sleep. On the other hand, Crick and Mitchison [66] considered REM sleep as a memory eraser, eliminating or reducing memories of unwanted behaviors.

Schmidt's [9] model of sleep function looked into how energy is utilized and allocated. In addition, he suggested that biologic processes need to be up or down regulated depending on specific biologic states (see Table 1).

7. Conclusion

It is clear that it is essential that birds and mammals including humans spend a considerable amount of time asleep. However, it is as yet unclear why sleep is required and maintained by evolution, and what factors influence the length and architecture of sleep-wake cycles in different species and at different times in the life cycle. Many attempts have been made to explain why we sleep and it has been demonstrated that lack of sleep has a profoundly negative effect on life. Current theories explore various aspects of sleep often based on observations made during sleep deprivation. However, there is no consensus as to the "core" function of sleep, if indeed there is only a single core function. Currently, there are few comprehensive and fully integrative functional studies explaining the molecular, structural, and electrophysiological functions of sleep. The quest to understand the various functions, and possibly the overall central or core function of sleep will continue and the findings of future studies will open new doors for approaching normal and abnormal sleep.

Conflict of Interest

All the authors declare to have no conflict of interest in this paper.

Table 1. Summary of common theories of the function of sleep*.

Author	Hypothesis	Summary of the theory	Drawback/strength
Meddis [43] and Webb [44,45] 1970s Siegel 2009 [46]	Adaptive, Immobilization or Ethological theory	<ul style="list-style-type: none"> • Function of sleep is to eliminate behavioral responsiveness during spare time when the organism is not well adapted. • It is an evolutionally designed survival strategy increasing safety and foraging behavior. • “Sleep instinct and circadian influence act to implement the behavioral strategy.” • Activities are scheduled for survival benefits. • Through evolution, some aspects of sleep may be intensified or eliminated based on the needs of the organism. • Sleep helps to preserve the rest phase of the sleep-inactivity cycle. • Prolonged sleep deprivation puts pressure on sleep inducing mechanisms and results in symptoms. 	<ul style="list-style-type: none"> • The proposed function can not be explained by sleep homeostasis and no physiological benefit was indicated. • Periods of simple rest could perform the same function without subjecting the organism to the dangers of sleep. • Sleep deprivation symptoms cannot be fully explained.
Moruzzi 1966 [58], 1972 [59]	Protective and Restorative theory	<ul style="list-style-type: none"> • We sleep to avoid exhaustion, and sleep functions for the recovery of the nervous system from synaptic use. • Sleep has a major role in the recovery from neuronal plasticity associated with learning and memory. • This is maintained by functionally integrated patterns of instinctive behavior. 	<ul style="list-style-type: none"> • Feedback mechanisms of sleep deprivation and homeostasis are loosely explained. • The physiologic benefits of the stages of sleep were not explained. • The nature of the recovery process was not elaborated.
Michel Jouvet 1975 [65]	REM sleep function Activity dependent genetically programmed	<ul style="list-style-type: none"> • The function of REM sleep is to “activate, select, instruct or release important motor activity.” • Neuronal activities that occur during REM sleep are important for proper maturation of genetically programmed behaviors. • Interactive genetic programming during REM sleep reinforces psychological individuation. • Sleep homeostasis during REM is more explained than NREM in this 	<ul style="list-style-type: none"> • Learned behaviors are not considered. • REM sleep is emphasized even though most animals spend more time in NREM sleep than REM sleep. • Recent studies have shown that NREM sleep is also tightly regulated which is also affected by sleep deprivation.

	innate behavior	theory.	
		<ul style="list-style-type: none"> • REM sleep occurs predominantly in infancy hence most of the neurologic development happens in that age. Presence of REM sleep in adulthood suggests REM sleep related networks are also necessary to maintain the behaviors at a mature level. • Activity dependent neuronal maturation occurs during REM sleep. 	
Adam 1980 [49] Oswald 1980 [50]	Restorative or Recuperative theory	<ul style="list-style-type: none"> • Sleep is a recovery and/or recuperative process • SWS functions for general body restitution and REM sleep functions as brain “repair.” • Sleep favors anabolism. 	<ul style="list-style-type: none"> • Total protein synthesis is greater during wakefulness. • Larger animals, which require higher protein synthesis have shorter sleep durations.
Francis Crick and Graeme Mitchison 1983 [66]	Function of REM sleep. (Reverse of activity dependent hypothesis by Jouvet [63])	<ul style="list-style-type: none"> • “The function of REM is to remove certain undesirable modes of interaction in the network of cells in the cerebral cortex.” • REM sleep regulation function is emphasized. • REM sleep is necessary for “unlearning “ or “reverse learning” of unwanted behaviors by removing “parasitic ” modes of neuronal interconnections. • REM sleep erases memory. 	<ul style="list-style-type: none"> • NREM sleep is not addressed in this theory.
Bergers and Phillips 1993, 1995 [47,48]	Energy conservation hypothesis	<ul style="list-style-type: none"> • Sleep conserves energy than quiet wakefulness. All biological functions are reduced during sleep. • The high demand of thermogenesis in endotherms is offset by reduction in metabolic rate during sleep. • Energy is conserved by sleep in response to decline in energy reserve. • “Sleep down-regulates body temperature and metabolic rate”. 	<ul style="list-style-type: none"> • The amount of energy conserved while asleep is relatively small. • REM sleep has a higher energy metabolism. • Sleep is distinct from torpor or hibernation.

James M. Krueger and Ferenc Obal 1993 [60]	Neuronal network reorganization or plasticity theory	<ul style="list-style-type: none"> • The function of sleep is to stimulate the “use, and thus maintenance of synapses unstimulated during wakefulness thereby serving to preserve the constancy of a synaptic superstructure important to brain organization.” • Function of sleep involves both REM and NREM sleep. Both states of sleep are regulated. Sleep reorganizes, maintains and reinforces unstimulated synapsis during waking. 	<ul style="list-style-type: none"> • Unclear why synaptic strengthening needs to happen “off line.” • Effect of sleep deprivation is not be fully explained.
J. Lee Kavanau 1994, 1996, 1997a,b [60-64]	Activity dependent sleep function (1994) and REM sleep function (1996)	<ul style="list-style-type: none"> • The function of sleep is to reinforce activity-dependent “enhancement of synaptic efficacy.” By spontaneous internally generated, non-utilitarian excitations occurring primarily during rest and sleep. • Behaviorally “non-utilitarian” neuronal activity associated with sleep is a mechanism for activity-dependent strengthening of synapses. Synapses strengthened are those that had been activated during waking. • REM sleep enhances memory. 	<ul style="list-style-type: none"> • Same as above.
Benington and Heller 1995, 2000 [53,54]	Restoration of brain energy metabolism	<ul style="list-style-type: none"> • Sleep deprivation results in increased EEG SWA in NREM sleep that is essential to the replenishment of cerebral glycogen stores that are progressively depleted during waking. 	<ul style="list-style-type: none"> • REM phenomena are not explained. • Studies in rats have shown that cerebral glycogen storage occurs only early during the sleep period. This finding questions the need for so many hours of sleep.
E Reimund 1994 [55]	The free radical flux	<ul style="list-style-type: none"> • High rate of metabolism during wakefulness accumulates free radicals that need to be cleared before neuronal damage occurs. • This theory assumes that during sleep, the brain has decreased metabolic rate. 	<ul style="list-style-type: none"> • This theory supports restorative sleep function • REM sleep that has a higher metabolic rate is considered as a component of sleep, not as a primary function of sleep.

Lulu Xie et al 2013 [57]	Neurotoxic clearance that results in sleep restorative function	<ul style="list-style-type: none"> • Sleep is associated with 60% increase in central nervous system interstitial space based on studies in mice. • Increased rate of amyloid clearance is observed. • Clearing of these neurotoxic products that are accumulated during the wake stage results in restoration of brain function. 	As above
Schmidt 2014 [9]	Energy allocation theory	<ul style="list-style-type: none"> • Behavioral strategies optimize utilization of energy to the maximum by shunting or diverting from other biological processes. The energy expenditure is partitioned across behavioral states. • Three phenotypes are described across evolution. <ol style="list-style-type: none"> 1. “Torpor”- highest energy saving with some physiologic functions compromised. 2. “Sleep-wake cycling” – up regulation and down regulation of biological function occur with phase cycling with overall energy conservation balance. Some critical functions occur at night so as to decrease energy need during wakefulness. 3. “Continuous or predominant wakefulness”- highest energy demand • During REM sleep, suspending thermoregulatory and skeletal muscle control saves energy and is allocated to other functions. • Cycling between REM and NREM sleep is governed by “thermal inertia” that is defined by size/surface area to volume ratios. 	<ul style="list-style-type: none"> • “Unifies” all the above theories. Incorporates evolutionary, behavioral state, energy utilization, “restoration and “restitution” theories • Quantification and significance of the energy shunted needs further study. • Could just resting fulfill the function? • Why does REM sleep get longer and longer over the sleep period? • Variations of sleep stages across age are not explained. • Why would the organism sacrifice so much of its lifetime in sleep to allocate energy rather than use other forms of energy conservation and allocation such as motor quiescence?

Listed here are some of the current theories on the purpose of sleeping. No claim is made that this list is exhaustive. Theories are lumped together when they resemble each other, although individual differences may remain. Readers are encouraged to read the original manuscripts for more details. *Note: some theories focus on the evolutionary aspects of sleep function, and others focus on the pathophysiologic effects of sleep deprivation.

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