Unveiling sleep mysteries: functions

Revelando mistérios do sono: funções

M. da Mota Gomes[1]

> "Methought I heard a voice cry "Sleep no more!
> Macbeth does murder sleep," the innocent sleep,
> Sleep that knits up the ravell'd sleave of care,
> The death of each day's life, sore labour's bath,
> Balm of hurt minds, great nature's second course,
> Chief nourisher in life's feast."
> **William Shakespeare´s Macbeth: Act 2, Scene 2**

ABSTRACT

Sleep occupies roughly one-third of human lives, yet it is still not entirely scientifically clear about its purpose or function. However, the latest research achievement concluded that sleeping has much more effect on the brain than formerly believed. Much of these studies are about the effects of sleep deprivation, and the glymphatic pathway initially identified in the rodent brain.

In this paper, it is presented some of the theories about sleep functions, besides a review of some physiologic function of sleep.

Now, it is accepted that sleep is involved with cleaning the brain toxins, physical restoration, information processing and recall, regulation, besides strengthening the immune system.

Sleep implies in a neuronal activity markedly different along with its phases. It is regulated by two parallel mechanisms, homeostatic and circadian. Besides, the sleep-waking cycle involves diverse brain circuits and neurotransmitters and their interaction is explained using a flip-flop model.

Several theories may help clarify the reasons human beings spend an important part of their lives sleeping such as those of Inactivity, Energy Conservation, Restorative, and Brain Plasticity.

Recently, it was emphasized the importance of the glymphatic system that is a waste clearence system that acts mainly during sleep support efficient removal of soluble proteins and metabolites from the central nervous system.

Indeed, sleep meet the needs of higher brain functions along with basic vital processes.

Keywords: sleep function, sleep theories, sleep deprivation, sleep restoration, glymphatic system.

RESUMO

O sono ocupa cerca de um terço da vida humana, mas ainda não é totalmente claro cientificamente o seu propósito ou função. No entanto, a mais recente pesquisa concluiu que dormir tem muito mais efeito no cérebro do que se pensava anteriormente. Muitos desses estudos são sobre os efeitos da privação do sono e o sistema glinfático inicialmente identificada no cérebro de roedores.

Neste artigo, são apresentadas algumas das teorias sobre as funções do sono, além de uma revisão de algumas funções fisiológicas do sono.

Agora, aceita-se que o sono esteja envolvido com a limpeza de toxinas cerebrais, restauração física, processamento e memorização de informações, regulação do humor, além de fortalecer o sistema imunológico.

O sono implica em uma atividade neuronal marcadamente diferente ao longo de suas fases. É regulado por dois mecanismos paralelos, homeostático e circadiano. Além disso, o ciclo de vigília envolve diversos circuitos cerebrais e neurotransmissores e sua interação é explicada por meio de um modelo de flip-flop.

Várias teorias podem ajudar a esclarecer as razões pelas quais o ser humano passa uma parte importante de suas vidas dormindo, como as de inatividade, conservação de energia, restauração e plasticidade cerebral.

Recentemente, enfatizou-se a importância do sistema glinfático agir principalmente durante o sono, que é um sistema de eliminação de resíduos para apoiar a remoção eficiente de proteínas e metabólitos solúveis do sistema nervoso central.

De fato, o sono atende às necessidades de funções cerebrais superiores, juntamente com processos vitais básicos.

Palavras-chave: função do sono, teorias do sono, privação do sono, restauração do sono, sistema linfático.

[1] Associate Professor, Institute of Neurology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence author:
Marleide da Mota Gomes, mmotagomes@acd.ufrj.br

INTRODUCTION

Sleep is a universal component throughout the animal kingdom, but there is enormous variation like rest and sleep states across it. Besides, sleep is a complex physiological process of an active state of unconsciousness that is primarily reactive to an internal stimulus[3]. Paradoxically, there is a strong selective pressure not to sleep. However, sleep is highly maintained across evolution[6]. In recent times, the latest research developments have concluded that sleeping has much more impact on the brain than formerly supposed. Besides, any organ is as susceptible to sleep deprivation as the brain. It is now known that sleep supports basic, as well as higher brain functions. Also, new scientific evidence demonstrates that sleeping can clear potentially harmful waste from the brain and keep its normal functioning.

SLEEP FUNCTIONAL IMPORTANCE AND MECHANISMS

The sleep functions are essential for many basic vital functions[17]. Besides, sleep has been demonstrated to improve memory recall, regulate metabolism, and reduce mental fatigue[4].

In short, Krueger et al.[7] propose that sleep serves as an immune function, reduces caloric use, restores brain energy, serves a glymphatic function, restores waking-induced performance degradation, and serves a connectivity function (neuronal/glial connectivity -plasticity)

The sleep function may be defined according to sleep measurement and the evolution, tissue organization levels, molecular mechanisms, and regulation of sleep[7].

Moreover, it is also known that sleep disorders are linked to poor health, including the progression of neurodegenerative diseases and reduced lifespan in humans. It is also recognized that sleep most likely evolved together with the emergence of a nervous system, but little is known about the conditions that led to the evolution of sleep and about how sleep regulates basic vital functions. Its widespread occurrence implies that sleep is important, besides there are experimentally proven positive effects of sleep on the motor learning and memory, and negative effects on long-term memory, working memory, attention, higher-order executive function, and various decision-making processes, both conspicuous and acute[1,4].

Sleep patterns are different and change over the first few years of human life. In mammalian sleep, duration also varies tremendously among different species[6].

The hypothetical determinants of sleep includes factors that are Ecological (negative regarding - Protection against predation, Enhanced mating success, Incompatibility with swimming, Thermoregulation, Need to forage for food, but positive for Adaptive inactivity), and also Intrinsic (Enhancement of memory consolidation, Complementation / compensation for sleep NREM, Activity-dependent rewiring of CNS, Energy conservation, Metabolic clearance, Sensorimotor tuning, and Synaptic homeostasis), as revised by Joiner[6].

It is remarkable that sleep is not uniform because it is divided into two major phases: non-rapid eye movement (NREM) and rapid eye movement (REM). Besides, each phase is further divided into cycles: NREM phase is further divided into N1, N2, and N3, this last one, of deep or delta wave sleep. The REM sleep has a tonic (parasympathetically driven) and a phasic component (sympathetically driven state). During an 8-hour sleep, the brain goes in and out of the REM period about 4 to 5 times. Current theories suggest that memory consolidation occurs primarily during the N2 stage, as stated by Brinkman and Sharma[3], besides it is known that the REM phase is responsible for dreaming and by body voluntary muscle paralysis[3]. Some studies proposed specific roles for sleep stages comprising REM, N3, and also sleep spindles (typical of stage N2 sleep) and implicated in learning and memory[1]. Assefa et al.[1] mention that some authors suggest that N3 and REM are essential for higher-level cognitive functions for survival.

More specifically, Vyazovskiy and Delogu[15] propose that NREM and REM sleep have different and harmonizing contributions to the overall function of recovery of sleep. These authors suggest that cortical slow oscillations arising from brain networks in NREM sleep permit information processing, synaptic plasticity, and prophylactic cellular conservation ("recovery process"). On the other side, periodic excursions into an activated brain state (REM sleep) appear to be preferably positioned to accomplish the "selection" of brain networks, which have benefited from the process of "recovery".

In particular, Watson and Buzsáki[16] stand that sleep has a combination of memory consolidation and homeostasis. This is based on the fact that while REM sleep contribute to the homeostatic by weakening of overactive synapses, a conspicuous and transient oscillatory rhythm called "sharp-wave ripple," non-REM rhythm, has an abundance of this activity and it is the "key player in the memory consolidation process…a brief (50–150 ms) electrical rhythm generated by an intrinsic self-organizing process in the hippocampus", as reported by Watson and Buzsáki[16]. In conclusion, Joiner[6] remembers that sleep deprivation firstly leads to a rebound in NREM sleep, and he suggests that NREM sleep is more significant than REM sleep.

Regulation of the sleep is justified by the two-process model[1] (**Figure 1**), that is one homeostatic process depending on sleep and wake (Process S) and other process controlled by the circadian pacemaker (Process C). The first, Process S, increases during wakefulness and declines during sleep. Regarding the second, core body temperature and melatonin rhythms are markers of Process C linked to the "biologic clock." The daily light-dark cycle conducts rhythmic fluctuations in the behavior and/or physiology run by a biological clock, which in mammals is placed in the suprachiasmatic nuclei. The circadian cycles built by this clock occur through nature and have a period of about 24 hours[14].

Besides, there are brain areas involved in sleep regulation: sleep generators centers and arousal regions with their neurotransmitters. The first includes the ventrolateralpreoptic nucleus (VLPO), and the second, the PPT/LDT nuclei (pedunculopontine-PPT and laterodorsal tegmental nuclei -LDT), and also tuberomamillary nucleus (TMN), raphe nuclei and locus coeruleus (LC), hypocretin-containing neurons in the lateral hypothalamus (LH). The VLPO neurons sleep related releases GABA and galanin that overpower firing of arousal system neurons. However, VLPO is also inhibited by the arousal systems neurotransmitters such as acetylcholine, norepinephrine and histamine.

Giving an account of these two systems (sleep and arousal), a current theory has proposed that they form a "flip-flop" circuit. There are factors that influence these transitions such as the internal factors, homeostatic sleep drive and circadian rhythms.

This "flip-flop" model is a bi-stable circuit. Saper et al., as recorded by Schwartz and Roth[11], suggested that this model of sleep-wake regulation involves two groups of mutually inhibitory components: one on the sleep side, and the other, on the arousal side. Each one inhibits the other, but the balance tilt to the stronger sideways (**Figure 2**).

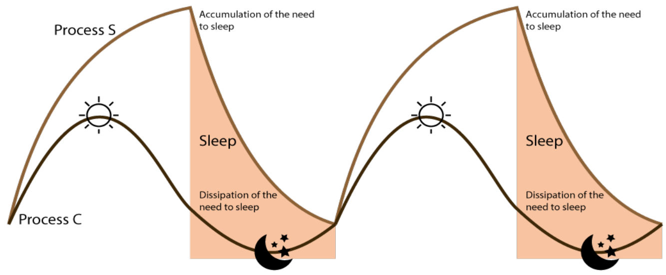

Figure 1. The two-process models of sleep regulation stimulation, one of the homeostatic process S and the other of the circadian process C.

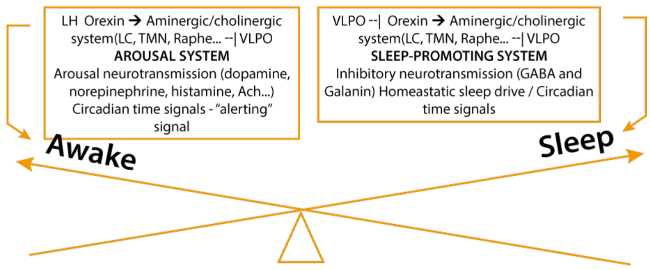

Figure 2. Schematic representation of the Flip-Flop Switch Hypothesis1[1] (---I indicates activity-suppressing, > indicates activity-promoting).

SLEEP FUNCTIONS

As a whole, it is easily perceived that good sleep makes the person feel better, and on the contrary, it makes people feel worse. This is a simple finding, but there are many questions regarding a single primary function of sleep or many (equally important) functions. In this way, studies are carried out to know what happens when humans or other animals are deprived of sleep. For instance, there are many studies about the effects of sleep deprivation on physical, neurocognitive and psychic function[1]. Other studies examine sleep patterns in a multiplicity of organisms to see if resemblances or dissimilarities amongst species might inform somewhat about sleep functions or sleep mechanisms oddities.

The studies of different forms of sleep disruption based on epidemiological and experimental data show disturbed physiology from subcellular levels to complex affective behavior. Also, an evolving consensus is that split sleep may be no less than damaging, as shortened sleep[13]. Besides, several studies were carried out to demonstrate the effects of total sleep deprivation. More recently, some studies show that the effects of "partial sleep restriction", more common than total restriction, they have the same results[4].

All these studies led to the reasons for sleep function, to be unfolded in the next sections. Indeed, there are numerous recent theories that have discovered the brain and try to recognize a determination for why sleep exists which contains the Inactivity theory, Energy conservation theory, Restoration theory, and the Brain plasticity theory[3] (**Figure 3**).

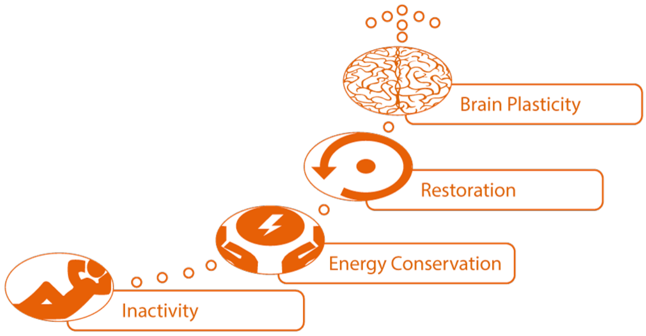

Figure 3. Functions theory of sleep

SOME HYPOTHESES AS TO THE OVERALL PHYSIOLOGIC FUNCTION OF SLEEP

Inactivity Theory or Adaptive, Immobilization or Ethological theory

The Inactivity theory is grounded on the concept of evolutionary pressure where beings that were inactive at night were not as much likely to die from predators or injury in the dark when they would be mainly defenseless. This would create an evolutionary and reproductive advantage to be inactive at night[3]. More particularly, in the adaptive inactivity, sleep serves a universal function, in convenient hours for each animal species. There was likely an evolutionary force for rest, allowing the body to preserve energy, and sleep attended as the extreme form of rest. However, the drawback is that it would always be safer to remain conscious to be able to react to an emergency.

Energy Conservation Theory

This theory considers that the main function of sleep is to decrease a person's energy need throughout part of the day and at night when it is least able to search for food[3]. Besides, metabolic rate decrease has been considered to be the mechanism by which sleep saves energy, comparable to torpor or hibernation[10].

It is important to remember that body temperature and caloric demand lower at the sleep time, and the metabolic rate reduces by around 15% and reaches a minimum in the morning in a standard circadian pattern[12], in comparison to wakefulness.

Schmidt[10] argues that the alternation of REM sleep with NREM sleep conserves energy by reducing the need to defend central core body temperature. These states reallocate the use of energy from the high demands of wakefulness in other essential sleep biological operations. In REM sleep, by removing thermoregulatory defense and skeletal muscle tone, there are peaks on the distribution of the energy to somatic and CNS-related functions, thus letting more energy resources to be devoted to specific biological events of REM sleep.

Restorative Theories

This theory considers that sleep permits the body to renovate and load cellular mechanisms required for biological roles that become decreased during the day. This is supported by the knowledge that many functions occur during the night, such as muscle repair, tissue growth, protein synthesis, and release of many of the important hormones for growth[3]. Slow-wave sleep (N3) functions for general body restitution and REM sleep functions as brain "repair."[1]. Besides, sleep favors anabolism and the active process of the glymphatic system that does not have time to perform that function when sleep is deprived. In this way, toxins can build up, and the effects will become apparent in cognitive abilities, behavior, and judgment[4].

Regarding these happenings, the glymphatic pathway (**Figure 4**), primarily active during sleep, is a fluid clearance system recently identified in the rodent brain. In them, the glymphatic pathway is primarily active throughout sleep, once the clearance of damaging metabolites such as amyloid β (Aβ) rises in the cortex for the duration of slow-wave sleep, comparative to the waking state, and two-fold relative to the waking state[2,9]. This glymphatic system is a glial-dependent perivascular network that subserves a pseudolymphatic function in the brain. Inside the glymphatic pathway, cerebrospinal fluid (CSF) go in the brain via periarterial spaces, after it comes to the interstitium via perivascular astrocytic aquaporin-4 (AQP-4), and then the system drives the perivenous drainage of interstitial fluid (ISF), finally clearing solutes from the neuropil into meningeal and cervical lymphatic drainage vessels. Recent MRI imaging and Pet studies in human has exposed that numerous features of the glymphatic and meningeal lymphatic systems likewise exist in humans[9].

It is known that sleep restores performance experimentally demonstrated and has obvious evolutionary value. However, there is an experimental lack of verified mechanisms for this restorative sleep role[7]. Although the build-up of adenosine in the brain is thought to be one factor that leads to our perception of being tired.

The previously mentioned glymphatic system function acts mainly during sleep and is largely disengaged during wakefulness. This is a macroscopic waste purification system that uses a specific system of perivascular tunnels encircled by astroglial cells, implicated on the waste of soluble proteins and metabolites from the central nervous system. Besides this function, the glymphatic system also helps the brain-wide supply of several composites, such as glucose, lipids, amino acids, growth factors, and neuromodulators.

Sleep offers a chance for the body itself to repair and to revitalize. This is additionally reinforced by results that many of the main restorative functions in the body like muscle growth, tissue repair, protein synthesis, and growth hormone release happen frequently, or in some cases only, throughout the sleep.

The CSF travels initially into the para-arterial space, then into an interstitial space over the APQ4 water channel pathway. Indeed, an exchange occurs between the CSF as well as the interstitial fluid due to rhythmic vascular pulsations during the various stages of sleep. Besides, during the sleep state, the CSF flows more profusely than during the day, and the interstitial space increases roughly sixty percent and effectively clears toxic cellular trash. Consequently, during sleep, the CSF removes the beta-amyloid metabolite in the brain accumulated during the day. It is shown that the deep non-REM sleep is the perfect sleep stage for the glymphatic system to function appropriately.

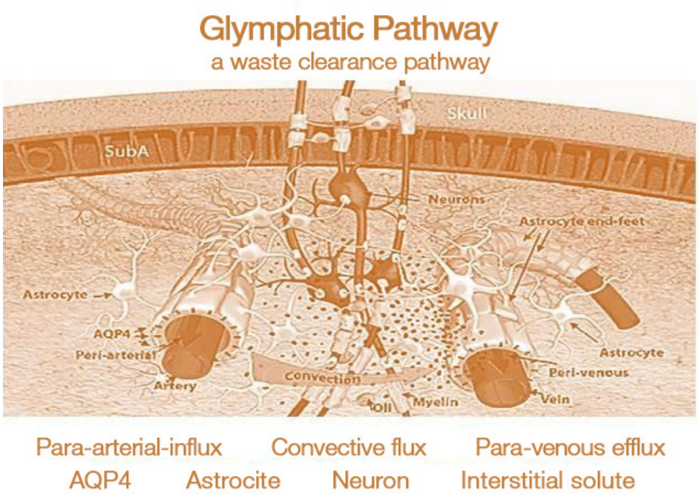

Figure 4. Glymphatic pathway and the probable most important function of waste clearance capacity by it (Adapted from Benveniste et al., 2019[2])

Brain Plasticity Theory

This theory establishes that sleep is needed for neural restructuring and growing of the brain's structure and function. This phenomenon is known as brain plasticity, but it is not entirely understood and it has several critical implications. There is experimental evidence that connectivity changes with sleep, sleep loss, and with altering afferent input, and that those alterations are related to sleep adjusting mechanisms. However, some authors believe that much refinement of ideas and innovative experimental approaches are needed to clarify the sleep-connectivity relationship[7]. It is more evident in the Brain Plasticity in infants and children as infants sleep upwards of 14 hours per day, and about half of that time is spent in REM sleep, the stage in which most dreams occur[3].

In adults, sleep is also important, as sleep deprivation have deteriorative effects on the ability to learn and perform a variety of tasks. Indeed, sleep is significant for neural plasticity. Neural plasticity mechanisms are important for sleep-dependent memory consolidation, and protein synthesis[8].

Moreover, it was demonstrated that sleep helps maintain basic brain functioning via a homeostatic mechanism that loosens connections between overburdened synapses, and that sleep aids build up and re-form significant memories[16].

The effects of Chronic Sleep Restriction were measured on the Brain Functional Network by local graph measures based on a set of task-based functional magnetic resonance imaging (fMRI) data. They were altered primarily across the limbic system (particularly in the hippocampus, parahippocampal gyrus, and amygdala), default mode network, and visual network[5].

CONCLUSION

It is still unclear the reason for sleep existence and function, and what factors influence the length and architecture of sleep-wake cycles in various species and at diverse life-cycle times. Sleep serves multiple purposes and, although it has been recognized that restriction of sleep has a deep negative effect on quality of life, it has been demonstrated that sleep washes the toxic waste products build-up.

In conclusion, all theories about sleep function presented are not extensive or complete. The prevalent ideas and various facets of sleep are often based on observations made during sleep deprivation. Indeed, it is more accepted that no single theory explains it all, and an association of them is more probable to hold the pivotal element to explain the sleep existence core.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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