4. Theories on the functions of sleep

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Summary

The beneficial effects of sleep are manifold. The present chapter provides knowledge on the function of sleep by an overview of the major principles and methodological approaches, as well as the leading theories in the field. Theoretical proposals range from the appropriate timing of activity (ecological hypothesis), through rest (energy conservation), recovery (detoxification, restoration of frontal lobe functions and mood), neural plasticity/memory consolidation (rapid eye movement sleep-centred hypothesis, two-stage model, system and synaptic consolidation), and neural network maintenance (reverse learning, neuronal group theory, dynamic stabilization, synaptic homeostasis hypothesis) to immune system functions (sleep-to-immune interactions). Several specific theories formulate similar conceptual backgrounds and predictions, whereas others are contradictory in terms of the nature and functional significance of sleep. The idea of a multilevel functional system is proposed, according to which the functions of sleep were multiplied during phylogeny, embedding the new evolutionary achievements of thermoregulation and complex central nervous systems.

KEYWORDS

adaptive immunity, adaptive inactivity, energy metabolism, executive functions, functional hypotheses, metabolic waste, mood regulation, synaptic downscaling, system consolidation

1 | INTRODUCTION

Rest–activity cycles are almost universal in the animal kingdom, providing the doubtless valuable adaptation of the organism to the geophysical cycles (Krueger et al., 2008; Rial et al., 2007). Rest simply means the lack or the reduced level of active behavioural adaptation, but it differs from the states sharing the phenomenological features of inactivity, like hibernation, torpor, and sleep. Beside motor rest, sleep—our current focus—is characterized by stereotyped and species-specific postures, increased sensory thresholds, homeostatic and circadian regulation, and eye closure, as well as a series of polygraphically measurable physiological traits (Nicolau, Akaârir, Gamundí, González, & Rial, 2000). Whether the complex traits of sleep are characterized by specific functions or reflect just the epiphenomenal aspects of the evolution of wakefulness is still a matter of debate, which can be most easily expressed by the following question: Does sleep have specific functions besides rest? (Rial et al., 2007). In the following section, the reader is provided with an overview of the proposed functions of sleep. Additional information on overall methodological approaches in studying the functions of sleep, as well as critical remarks regarding the issue of the functional significance of sleep, is presented. Given the complexity of the issue and the multiplicity of theories, in-depth analysis and critique of single theories is beyond the scope of this chapter; however, convergent and divergent predictions of the theories are occasionally addressed and discussed.

2 | OVERALL NOTES ON THE PROPOSED FUNCTIONS OF SLEEP

The list of the hypothesized functions of sleep is a long one. Mammalian sleep is a complex process with multiple macro- and microstates, and several physiological processes involved. Given the fact that most of the functional hypotheses are not mutually exclusive, the potential multiplicity of functions is a reliable version of the story (Table 1).

There are specific issues that have to be defined when studying the functions of sleep. For example: Who uses sleep? Is it the organism or is it some group of interrelated neurons? Are there specific functions for non-rapid eye movement (NREM) and rapid eye movement (REM) sleep or do they act in union? Is any beneficial effect of sleep also a function of it? For example, a good meal could result in better mood, but no physiologist would claim that a function of eating is mood restoration. Thus, the various proposals for the functions of sleep could complement each other, but may also reflect a common process with multiple phenomenological facets.

3 | SLEEP VIEWED AS ADAPTIVE INACTIVITY: ECOLOGICAL HYPOTHESES

Sleep is assumed to provide inactivity during periods when chances for active, behavioural adaptation are relatively low. Humans and other diurnal animals sleep at night, when continued activity has decreased survival value at least in natural circumstances (Webb, 1974).

A more recent version of this theory proposes that sleep is a variant of dormant states that is highly adaptive because it optimizes the timing and duration of behaviour (Siegel, 2009). This hypothesis is supported by the evidence suggesting that ecological variables are the most important determinants of sleep. Although the dualism of sleep (NREM and REM) is a particularly striking feature of it in almost all mammals and birds, this aspect is not explicitly focused on in the above theories. In addition, unihemispheric sleep in aquatic mammals (e.g., in the bottlenose dolphin) or in some species of birds indicates that slow-wave sleep is mandatory even in ecological circumstances that are incompatible with behavioural sleep (motor rest) (Mascetti, 2016). The bottlenose dolphin is adapted to the maintenance of constant locomotion for long periods because of repeated episodes of voluntary breathing when surfacing and opening its blowhole through muscle contraction. Yet, these aquatic mammals still manifest sleep-like slow waves, albeit unihemispherically: the functions of the sleeping hemisphere are compensated by the wakeful one, characterized by low-amplitude fast electrical activity. Likewise, migrating birds do not have the possibility to remain behaviourally quiet for long periods, but they express unihemispheric slow-wave sleep as some aquatic mammals do. That is, in spite of the strong evolutionary and ecological forces against sleep, the processes characterizing slow-wave sleep did not disappear, but became adapted to the circumstances. These findings draw the attention towards the utmost importance of slow waves of sleep in understanding the functions of sleep.

4 | REST AND ENERGY CONSERVATION (ENERGY HOMEOSTASIS) AS A FUNCTION OF SLEEP

There are phylogenetic correlations between sleep, endothermy, and metabolic rates. These and several other findings based on the interindividual differences-type of approaches suggest that sleep evolved in order to save energy (Walker & Berger, 1980). The brain is an organ, which weighs only 2% of the adult human body mass, yet consumes around 20% of the total oxygen of the body. The energy and oxygen consumption of the brain decreases during sleep. The most dramatic decrease is seen during slow-wave (N3) sleep: up to 40% decrease in cerebral glucose metabolism and around 25% decrease in oxygen uptake was reported in adult human subjects. In contrast, levels of metabolic activity and oxygen consumption measured during Stage 2 sleep (N2) and REM sleep did not significantly differ from wakefulness (Madsen & Vorstrup, 1991; Maquet, 1995). Sleep in general and slow-wave sleep in particular are associated with body cooling (decrease in core body temperature) (Harding, Franks, & Wisden, 2019). Lack of sleep is associated with increased energy expenditure (Jung et al., 2011; Markwald et al., 2013) and decreased glucose tolerance (Spiegel, Leproult, & Van Cauter, 1999). These findings support the theory proposing that energy conservation is one of the potential functions of sleep (Berger & Phillips, 1995; Walker & Berger, 1980). It has to be noted, however, that torpor and hibernation are significantly more effective in this term, and both are characterized by a striking lack of sleep-like cerebral activity (Harding et al., 2019). Thus, sleep is less effective in terms of energy conservation and more complex in terms of brain activity than should be expected on the exclusive predictions of the energy conservation theory. In addition, the majority of sleep time consists of Stage 2 and REM sleep, which are ineffective in terms of energy conservation (saving); thus the complexity of sleep was left largely unaddressed by these theories.

KEY POINTS

- Ecological hypotheses: we sleep in order to optimize the timing and effectivity of our activity.
- Energy conservation: we sleep in order to save energy.
- Recovery hypotheses: we sleep for the removal of metabolic waste and restoration of our neurocognitive as well as emotional functions.
- Memory consolidation and immunity: we sleep in order to strengthen our memories and adaptive immunity.
- Neural network hypotheses: we sleep in order to maintain our neural networks.

LEARNING OBJECTIVES

- The reader learns the major principles and methodological approaches relevant for studies pursuing the functions of sleep.
- Major theoretical proposals for the functional significance of sleep are followed.
- The comparison of the major theories explaining the functions of sleep is attained.

TABLE 1 Theories on the functions of sleep

Meta-theories	Specific theory	Core statement	Reference
Ecological hypotheses	Adaptive theory of sleep	Sleep is adaptive non-responding	Webb (1974)
	Adaptive inactivity	Sleep optimizes the timing and duration of behaviour	Siegel (2009)
Sleep as rest	Energy conservation	Sleep evolved to offset the high energetic cost of endothermy	Walker & Berger (1980); Berger & Phillips (1995)
	Adenosinergic theory	The core of sleep need is probably related to primitive functions of life, like energy metabolism	Porkka-Heiskanen & Kalinchuk (2011)
Sleep as neuronal detoxification and restitution	Sleep as detoxification	Sleep removes toxins and metabolic waste	Ishimori (1909); Piéron (1913); Inoué et al. (1995); Xie et al. (2013); Varshavsky (2019)
	Recovering prefrontal cortical functions	Prefrontal cortical recovery occurs during human slow-wave sleep	Horne (1993)
	Mood restorative function of REM sleep	REM sleep is involved in active mood regulation	Cartwright et al. (1998); Goldstein & Walker (2014)
Learning/memory consolidation	REM sleep memory consolidation	REM sleep contributes to memory consolidation by cortical activation	Smith (1995); Smith (1996)
	Two-stage model of memory formation	NREM sleep contributes to memory consolidation by reactivation indexed by hippocampal sharp-wave ripples	Buzsáki (1989); Buzsáki (1998)
	System consolidation and synaptic consolidation	NREM sleep restructures representations; REM sleep strengthens specific synapses	Diekelmann & Born (2010); Born & Wilhelm (2012)
Neural network maintenance	Reverse learning theory (REM)	REM sleep removes parasitic modes of network functioning	Crick & Mitchison (1983)
	Neuronal group theory	Sleep maintains synaptic infrastructure and incorporates novel stimulus patterns into a synaptic contextual network	Krueger & Obál (1993); Krueger & Obal (2003)
	Dynamic stabilization of neural circuitry	Sleep maintains infrequently used but vital synapses by non-utilitarian activations during sleep	Kavanau (1994); Kavanau (1996)
	Synaptic homeostasis hypothesis	Slow-wave sleep renormalizes the net increases in synaptic strengths during wakefulness (synaptic downscaling)	Tononi & Cirelli (2003); Tononi & Cirelli (2014)
Immunological theory of sleep	Sleep-to-immune directionality	Slow-wave sleep improves adaptive immune response and stable immunological memory formation	Besedovsky et al. (2019)

Abbreviations: NREM, non-rapid eye movement; REM, rapid eye movement.

An alternative version of the energy conservation hypothesis of sleep is related to the nucleotide adenosine, a breakdown molecule of the universal energy molecule adenosine triphosphate (ATP). Neural activity is clearly energy dependent; thus it is followed by the increase of adenosine in the extracellular space. Receptors of adenosine are inducing or facilitating sleep, mainly by the inhibition of the cholinergic basal forebrain arousal system (Porkka-Heiskanen & Kalinchuk, 2011). Again, REM sleep is non-functional from this point of view, as it is characterized by high levels of brain activity and metabolism.

5 | NEURONAL DETOXIFICATION AND RESTITUTION: FROM CHEMICAL TO BEHAVIOURAL ASPECTS

Sleep might be more than rest. It could be involved in active restitution processes aiming to restore the psychophysiological variables to a hypothetical baseline or an optimal value. Several theories on the functions of sleep hypothesize specific recovery-type processes during sleep. Here we address those that are mainly and primarily recovery like, but will discuss the ones that are based on complex neural network maintenance in a separate subchapter.

5.1 | Sleep viewed as detoxification

The proposed detoxification function of sleep finds its roots in the early hypnotoxin theories of Ishimori (1909) and Piéron (1913). These theories hypothesized that the cause of sleep is the accumulation of some toxic, sleep-inducing compound in the central nervous system, which was called hypnotoxin by Piéron (1913). Both researchers were able to transfer the hypothesized sleep toxin from donor to recipient animals, but it took several decades, almost a century, to find some chemically identifiable endogenous "toxins" of sleep. Some of

the research work pursuing this question reported that uridine and oxidized glutathione are components of the so-called sleep-promoting substance derived from the brain tissue of sleep-deprived rats. Uridine may facilitate the inhibitory neurotransmission at the synaptic level of the gamma-aminobutyric acid $(GABA)_A$-uridine receptor complex, whereas oxidized glutathione may inhibit the excitatory neurotransmission at the synaptic level of the glutamate receptor. The latter effect is associated with neuroprotection against neurotoxic and oxidative damage, which was reported to reflect a potential revival of the Ishimori-Piéron hypnotoxin theory (Inoué, Honda, & Komoda, 1995).

Recent findings are coherent with the hypnotoxin theory as well. Sleep facilitates bulk cerebrospinal fluid transport and the clearance of toxic metabolites (Xie et al., 2013). "The energetic costs of bulk convection are largely independent of metabolite concentrations; thus, it is more efficient to wait for metabolic waste to 'build up' before engaging in an expensive new round of convective clearance" (Anafi, Kayser, & Raizen, 2019). Similar views were expressed in the context of the fragment generation hypothesis, suggesting that a major function of (NREM) sleep is the accelerated removal of protein fragments (Varshavsky, 2019). These findings and the related theories may shed new light on the nature and functional significance of sleep in the near future and may support the validity of the hypnotoxin theory proposed by Ishimori (1909) and Piéron (1913).

5.2 | Human slow-wave sleep recovers prefrontal cortical functions

Although waste clearance theories of sleep are intriguing, empirical findings are still scarce and the level of analysing sleep phenomena should involve the measures and indexes we use to objectively define and characterize sleep in the laboratory (e.g., electroencephalogram [EEG] slow waves). In other words, rest and restitution have to be evidenced on the system level as well. Horne (1993) noted that cortical recovery, if it exists in sleep, is most likely to occur during human slow-wave sleep and in the prefrontal cortex. Thus, whatever goes on at the cellular level during sleep, the system and the behavioural level indicate a strong link between slow-wave sleep and frontal lobe functions in human subjects. Neuropsychological evidence suggests that sleep deprivation induces a reversible dysfunction of the frontal lobes. The critical part of sleep involved in this effect is the one characterized by EEG slow waves. Slow-wave activity dominates the human frontal EEG leads in topographical terms. Unlike sleep deprivation-induced decreases in vigilance, the sleep loss-related frontal lobe dysfunction symptoms cannot be effectively compensated for by extra motivation or stimulants. Sleep loss-induced decreases in verbal fluency (finding words or verbs beginning with a given letter), non-verbal planning (solving tasks like the Tower of Hanoi), originality, remembering the order of events, and complex reasoning, as well as increases in susceptibility to interference (distraction by irrelevant stimuli) and apathy, cannot be compensated for and are hypothesized to reflect the functional significance of sleep. These tasks and behavioural phenomena are tightly related to the proper functioning of the frontal lobes and are considered as items of the core dimension of sleepiness. In contrast, the so-called optional sleepiness reflects the changes in the motivational basis of behaviour during sleep deprivation. That is, subjects aim to get to sleep and are not interested in solving the tasks (Horne, 1991). Slow waves are present even in aquatic mammals and migrating birds in forms of unihemispheric sleep, indicating their indispensable role in the maintenance of mammalian and avian central nervous system function. The vulnerability of the human frontal lobes to sleep loss could be explained by their indispensable function in coordinating wakeful cognitive processes. Constant activity leads to greater exhaustion, and thus more prominent sleep debt.

5.3 | The mood/emotional reactivity regulatory functions of REM sleep and dreaming

Several findings indicate the active role of REM sleep in mood restoration and emotional regulation. Negative mood states in healthy volunteers imply negatively toned dreams early in the night, but successive REM periods are characterized by progressive mood improvement until early morning. Such effects are not seen in subjects with positive evening mood states: these subjects are characterized by maintained positive mood during successive dream episodes of REM sleep (Cartwright, Luten, Young, Mercer, & Bears, 1998). Additional evidence and theoretical modelling indicate that REM sleep-related reactivation of recent memories in the neurochemical context characterized by dramatically reduced adrenergic tone leads to a long-term strengthening of salient memories, yet a dissipation of the emotional charge. "Thus, sleep transforms an emotional memory into a memory of an emotional event, that itself is no longer emotional" (Goldstein & Walker, 2014). It has to be noted however, that the experimental data supporting this latter conclusion are ambiguous. Mood induction before learning and recall can cause emotional interference (also known as mood state-dependent memory). That is, recall performance is lower if mood states are different during learning and retrieval. Emotional interference is equal in settings characterized by NREM and REM sleep-dominant retention intervals, in spite of the fact that REM sleep is hypothesized to play a pivotal role in emotional decontextualization (Deliens, Neu, & Peigneux, 2013). Rather several full sleep cycles are needed for an effective emotional decontextualization in this paradigm (Deliens, Gilson, Schmitz, & Peigneux, 2013; see further details in Chapter A. 5. Sleep and psychology).

6 | SLEEP, MEMORY, AND PLASTICITY

Sleep has been known for a long time to be superior in terms of memory retention as compared to wakefulness (Jenkins & Dallenbach, 1924). Early works emphasized several factors mediating this finding, amongst which reduced interference during sleep was a prominent one, but later the idea of the sleep-related enhancement of

memory consolidation (strengthening of memory trace) emerged in several forms and proposals.

6.1 | The REM sleep memory consolidation hypothesis

Although NREM sleep precedes REM sleep in the natural sleep cycle of the adult human, historically REM sleep was the first one that was thought to be involved in sleep-related memory processing, whereas NREM sleep was considered as a phase of rest and restitution. The peculiar nature of REM sleep, characterized by increased cortical activation in spite of apparently deep sleep in terms of muscular tonus, led several researchers to the assumptions that this state is involved in the active, offline processing of the information acquired during presleep wakefulness, increasing the consolidation of memories (Fishbein, 1971; Moruzzi, 1966). Major evidence came from animal studies reporting clear postlearning increases in percentage of REM sleep during specific time windows (so called REM windows), whereas REM sleep deprivation during the REM windows interferes with memory consolidation. Excess REM times normalize in parallel with the acquisition of the task (Smith, 1995). Indeed, REM sleep-related cholinergic activity and protein synthesis turned out to be critical factors involved in REM sleep-related postlearning synaptic plasticity enhancements in rats (Smith, 1996). In addition, artificial increase of cortical activation during postlearning REM sleep, but not slow-wave sleep, by electrical stimulation of the mesencephalic reticular formation enhanced memory consolidation (Hennevin, Hars, & Bloch, 1989). Such interventions are known to enhance long-term potentiation of dentate gyrus synapses in rats, which suggests a clear link with the cellular processes involved in memory formation and learning (Bloch & Laroche, 1985).

Some early evidence was reported in human studies as well; however, the overall support remained weak and the methodological issues raised several questions. Later on, evidence suggested that the consolidation of procedural, but not declarative, memories is associated with postlearning REM sleep in humans (Smith, 2001). For example, the acquisition of probabilistic rules results in learning-related reactivations of specific neural networks during postlearning REM sleep, in a learning- and acquisition-dependent manner (Peigneux et al., 2003). Moreover, REM sleep deprivation affected the overnight improvement of a visual-perceptual skill, whereas NREM sleep-related awakenings had no effect (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994). However, the overall evidence still suggests a mixed contribution of both NREM and REM sleep to procedural memory consolidation. In addition, the term procedural was loosely defined in many of these studies, thus the specific involvement of REM sleep in procedural memory consolidation is far from being revealed (see further details in Chapter A. 5. Sleep and psychology).

Besides the involvement of REM sleep in procedural memory consolidation (offline gains), there is evidence for its facilitatory/modulatory effect on emotional declarative memory consolidation (Gilson et al., 2016; Wagner, Gais, & Born, 2001). It has to be noted, that animal studies relied on emotional memories, because of evident methodological and phylogenetical reasons (captive laboratory animals are motivated by using positive or negative incentives to learn the tasks, and consequences of non-learning are evidently negative, especially when compared to humans). Thus, the early findings reported as being supportive for the REM sleep memory consolidation hypothesis might find their link with the newer ones along this route.

Besides empirical support, the REM sleep memory consolidation hypothesis has particularly severe critics. The reported effects were hypothesized to reflect stress, instead of learning. Also, humans suffering long-term reductions of REM sleep as a result of pharmacological treatment with irreversible monoamine oxidase inhibitors or brain lesions do not show memory deficits (Siegel, 2001). It has to be determined whether these latter inconsistencies imply a substantial revision of the theory or reflect some compensatory processes that were not formerly considered, but are central to the treatment effects of the REM sleep-suppressing drugs.

6.2 | The two-stage model of memory formation and its relevance for the functions of sleep

In spite of the surge around the potential involvement of REM sleep in memory consolidation, there are some early reports on the importance of slow-wave, but not REM, sleep in declarative memory consolidation in humans (Fowler, Sullivan, & Ekstrand, 1973). The potential involvement of slow-wave sleep in declarative memory consolidation was replicated several times, by comparing early (slow-wave sleep-dominated periods) and late (REM phase-dominated periods) sleep in terms of memory consolidation (Plihal & Born, 1997). These findings were indeed neurophysiologically grounded and contextualized by the two-stage model of memory formation (Buzsáki, 1989; Figure 1). According to this latter theory, the first stage of memory formation is characterized by hippocampal rhythmic slow activity during behaviourally active wakefulness and is supported by the transmission of perception-induced neuronal activity patterns from the sensory and association areas of the neocortex to the Cornu Ammonis (CA)3 region of the hippocampal formation through the perforant path in the superficial layers of the entorhinal cortex. Consequently, CA3 pyramidal neurons become primed for firing in the second stage of memory formation taking place during behavioural quiescence and NREM sleep. In this second stage the primed CA3 pyramidal neurons initiate firing. The firing pattern is identical to the one seen during the first stage, when these CA3 hippocampal neurons were targets of neocortical synaptic bombardment, but it is significantly speeded up. Patterned firing of CA3 pyramidal neurons is transmitted to the neurons of the hippocampal CA1 region, which relay to the neocortex through the deep layers of the entorhinal cortex. The second stage is characterized by hippocampal sharp-wave ripple complexes in electrophysiological terms. The result is a long-term, neocortically based engram, which gets free from its

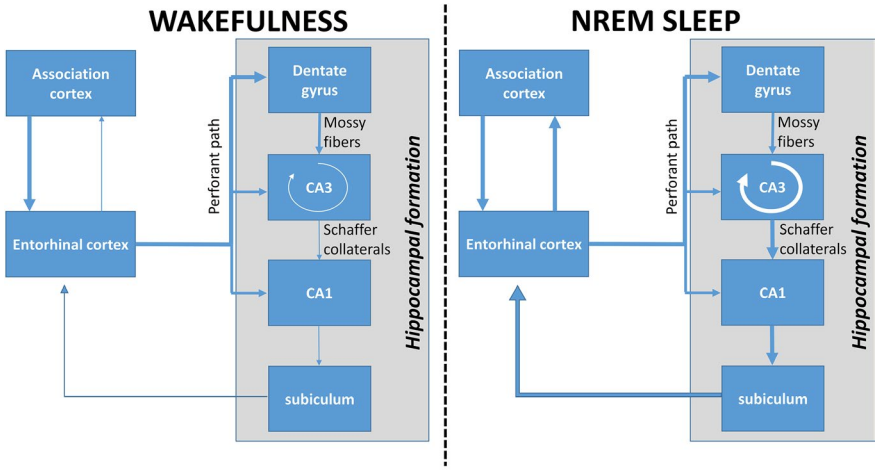

FIGURE 1 Pathways and information flow supporting the two-stage model of memory formation. During active wakefulness the neural codes of the neocortical structures are forwarded to the hippocampal formation through the entorhinal cortex and the perforant path. During non-rapid eye movement (NREM) sleep, the recurrent collaterals of the Cornu Ammonis (CA)3 region of the hippocampus actively replay the hippocampal neural codes to the neocortex, through the Schaffer collaterals, the CA1 region and the subiculum. Thick arrows indicate stronger information flow. Figure adapted from the works of Axmacher, Mormann, Fernández, Elger, and Fell (2006) and Hasselmo (1999)

temporary hippocampal roots. NREM sleep is hypothesized to be involved in this process, as it is characterized by sharp-wave ripple complexes (Buzsáki, 1998), which were indeed shown to be associated with neocortical sleep spindles and the up states of the sleep slow oscillation of cortical origin.

There is strong empirical evidence supporting this theory, ranging from the already mentioned relationship between slow-wave sleep and declarative memory (Plihal & Born, 1997), through the involvement of sleep-spindle related processes in memory consolidation (Kaestner, Wixted, & Mednick, 2013), to the direct experimental evidence supporting the active role of sharp-wave ripple complexes in the memory of rodents (Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009). It has to be noted, however, that sharp-wave ripple oscillations during slow-wave sleep were found to induce long-term synaptic depression, thus their memory-enhancing effects could reflect memory engram refinement instead of (just) strengthening the relevant synapses (Norimoto et al., 2018; see also the synaptic homeostasis hypothesis below). In addition, NREM sleep was found to be involved in the consolidation of motor procedural (Fogel et al., 2017) and visual perceptual (Gais, Plihal, Wagner, & Born, 2000) memories as well (see further details in Chapter A. 5. Sleep and psychology). However, these latter processes are not assumed to involve the hippocampo-neocortical dialogue described in the two-stage model of memory formation.

6.3 | System consolidation followed by synaptic consolidation

Reactivation of recently acquired memories during NREM sleep results in stable memory traces, which are, however, parts of the overall mnemonic system (new memories are related to old ones). That is, the new memory trace becomes embedded in the dense network of previously acquired memories in neocortical stores. Instead of a simple strengthening, this process is a redistribution of representations between different neuronal systems, called system consolidation (Diekelmann & Born, 2010). It has to be noted that not all memories are strengthened during sleep. There is evidence for a selection process, based on assumed future relevance, which can be experimentally manipulated in humans (Born & Wilhelm, 2012). System consolidation means a qualitative change in the memory trace; thus it is different from synaptic consolidation, which is hypothetically attributed to REM sleep. The latter sleep phase is characterized by a neurophysiological, neurochemical milieu promoting long-term potentiation (see also the REM sleep memory consolidation hypothesis) of the synapses, which were already formed and primed during the system consolidation phase of NREM sleep (Diekelmann & Born, 2010).

7 | BEYOND MEMORY CONSOLIDATION: THE OVERALL MAINTENANCE OF NEURAL NETWORKS DURING SLEEP

The rich EEG/polygraphically recordable phenomena associated with the different sleep states are most prominent in species with a complex central nervous system (ganglia). It is thus logical to assume that the physiological phenomena we record in human sleep laboratories find their function in the complex networks of the central nervous system. Accordingly, several theoretical proposals aim to catch this aspect of the function and functional significance of sleep. These theories might overlap significantly with several other theories on the functions of sleep, but are different in terms of their network-based approach, specific predictions, and implemental openness.

7.1 | REM sleep as reverse learning

Reverse learning or unlearning is a hypothetical process during which the brain removes unwanted information and weakens connections that are supporting useless, parasitic modes of functioning. The restorative and memory consolidation functions of NREM sleep are acknowledged, but not focused on by the authors of the reverse learning theory (Crick and Mitchison, 1983). Reverse learning is hypothetically attributed to REM sleep, which is peculiar in terms of intense neuronal activity and energy usage, which is clearly non-coherent with rest and energy conservation. Reverse learning theory was proposed by Crick and Mitchison (1983) on a theoretical and speculative background with the aim of explaining the internally generated, random, self-activation of the brain during REM sleep, which was hypothesized to function as a mechanism, which frees the neuronal networks from overload that emerges during wakefulness. Large, overlapping and superimposed storage in mammalian neuronal networks may induce parasitic modes of network functions. The authors "suggest that in REM sleep we unlearn our unconscious dreams," "we dream in order to forget" (Crick & Mitchison, 1983). The theory was maintained without additional empirical evidence, on a purely theoretical basis for years (Crick, 1988; Crick & Mitchison, 1995), until the emergence of the synaptic homeostasis hypothesis, which proposed similar functions for NREM sleep (Tononi & Cirelli, 2003; see below), as well as the discovery of the REM sleep-active melanin-concentrating hormone containing neurons' involvement in active forgetting in the posterior hippocampi of mice (Izawa et al., 2019). Thus, the long-postulated mechanism of reverse learning during REM sleep got its first physiologically meaningful form: the theory is worth considering again, at least in terms of hippocampal networks. It has to be mentioned, however, that the reverse learning theory is in sharp contrast to the REM sleep memory consolidation hypothesis and the synaptic consolidation mechanism, both of which suggest that REM sleep is indeed involved in memory consolidation/strengthening, not forgetting/weakening. There are large amounts of controversial data supporting or disproving the REM sleep memory consolidation theory and very little empirical research testing the reverse learning theory; thus it is somewhat early to directly compare their validity. It has to be noted, however, that indirect evidence suggests the involvement of REM sleep hippocampal rhythmic slow activity in the active weakening of transiently stored hippocampal memories, which were already transferred to long-term neocortical stores (Poe, Nitz, McNaughton, & Barnes, 2000). Thus, REM sleep-related reverse learning in the hippocampal formation (see also Izawa et al., 2019), together with a suggested neocortically-based synaptic consolidation, is a theoretically plausible scenario.

7.2 | The neuronal group theory sleep function

Several findings support the idea that sleep is an emergent property of the central nervous system. The neuronal group theory of sleep function was indeed the first one that explicitly assumed that sleep is local and is initiated in neuronal groups as a function of prior usage/input during wakefulness. High usage of the neuronal group by sensory or internally generated inputs induces the release of somnogenic cytokines (interleukin 1 beta and tumor necrosis factor alpha) and growth factors (brain derived neurotrophic factor), altering receptor sensitivity in a paracrine fashion. These events are initiated by energetic demands (ATP release) and are involved in the local initiation of a sleep-like (disjunctive) state of the neuronal group. The disjunctive state is characterized by autonomous oscillatory activity resulting in maintenance of synaptic infrastructure and incorporation of novel stimulus patterns into a synaptic contextual network (Krueger & Obál, 1993; Krueger & Obal, 2003; Krueger et al., 2008). The maintenance of synaptic infrastructure is envisioned to consist of membrane events resulting in "amplified strength of synapses infrequently used during wakefulness" (Krueger, Obál, Kapás, & Fang, 1995). Thus, "sleep serves to reinforce certain synapses relative to others." (Krueger et al., 1995). REM sleep is viewed as a brainstem and spinal cord level of neuronal reorganization, thus resulting in serious autonomic disturbances, such as loss of thermoregulation and baroreceptor sensitivity (Krueger et al., 1995).

7.3 | The dynamic stabilization of neural circuitry

Infrequently used synapses may code information that is critically important from the point of view of adaptive strategies and survival. Infrequent use might result in the breakdown of synaptic efficacy, which can be deleterious. Thus, offline periods allowing the internal activation of these synapses without the interference with ongoing behaviour, are useful and critical and called the dynamic stabilization of neural networks. This is in fact considered the main function of sleep. REM sleep is specific in terms of the dynamic stabilization of motor circuits in homeotherms, because high basal metabolic rate would result in significant motor output during this process. Thus, muscular atonia is considered a core feature of REM sleep in this theoretical framework (Kavanau, 1994, 1996). This latter concept echoes the classic theory of Michel Jouvet, proposing that the function of REM sleep is an iterative neurological programming that works to preserve an individual's psychological heredity, in spite of neural plasticity processes that might work against this. Muscular atonia provides a safe physiological condition for this network activation initiated by ponto-geniculo-occipital (PGO) spikes (Jouvet, 1998).

There is a partial coherence between the claims of the neuronal group theory and the dynamic stabilization theory of sleep. Both suggest that sleep evolved in order to maintain the synaptic infrastructure of the central nervous system. However, unlike the neuronal group theory, the dynamic stabilization theory does not explicitly assume a local sleep phenomenon or a bottom-up type of synaptic use-dependent sleep regulation.

7.4 | The synaptic homeostasis hypothesis of sleep

Synapses are strengthened during wakefulness as a result of the neurochemical milieu characterized by the continuous release of noradrenaline. The overall increase in synaptic strength, resulting in increased energy and space costs, as well as in decreased signal-to-noise ratio, urges a renormalization process. The latter is called synaptic downscaling and is hypothesized to take place during NREM sleep thanks to the low frequency rhythm provided by sleep slow waves (Figure 2). New information coded during presleep wakefulness is maintained, because the differences in synaptic strengths are kept constant during downscaling (Tononi & Cirelli, 2003, 2014). Although there is a partial convergence in terms of the maintenance of synaptic infrastructure suggested by the neuronal group theory and the dynamic stabilization theory, the predictions of the synaptic homeostasis hypothesis are partially different and somewhat more explicit. Thus, according to the synaptic homeostasis hypothesis function of sleep, episodes of slow-wave sleep are followed by reductions in the net synaptic strengths. Such predictions are much easier to test than the ones referring to a vaguer concept of synaptic infrastructure maintenance or infrequently used synapses with vital importance.

A further important issue emerges when we compare the synaptic homeostasis hypothesis with the memory consolidation hypotheses of sleep. It is evident that the former predicts generally decreasing synaptic strengths, whereas the latter assumes increasing synaptic strengths in specific cortical synapses. By citing data that do not align with the hippocampal replay concept, Tononi and Cirelli (2014) argue against NREM sleep-related synaptic potentiation, favouring the downscaling-dependent increase in signal-to-noise ratio, memory selection and gist extraction as key factors in the beneficial effects of sleep on memory. However, there is direct evidence for neuronal reactivation and branch-specific spine formation during NREM sleep following the execution of motor-learning tasks in mice (Yang et al., 2014). This finding clearly contradicts the predictions of the synaptic homeostasis hypothesis.

Evidence supporting the synaptic homeostasis hypothesis of sleep is mostly indirect (e.g., increases in glucose uptake after wakefulness and decreases after sleep, and reflecting the energy costs of different levels of net synaptic strengths). A direct test of the synaptic homeostasis hypothesis is the measurement of the overall firing rate of neurons before, during, and after sleep. Findings of such experiments indicate a complex picture providing only partial support for the central assumptions of the synaptic downscaling process during slow waves. That is, in contrast to the predictions of the synaptic homeostasis hypothesis, the firing rate of the slow-firing hippocampal neurons increases after a period of sleep in rats. Such a finding would be predicted by the dynamic stabilization theory, but not the synaptic homeostasis theory of sleep function. In contrast, the spike rate of the fast spiking hippocampal neurons was found to decrease after a period of sleep. This latter finding is in agreement with the synaptic homeostasis hypothesis. However, a further unexpected finding of this study was that the reduction of firing rates of hippocampal pyramidal neurons occurred during REM, but not slow-wave sleep (Grosmark, Mizuseki, Pastalkova, Diba, & Buzsáki, 2012). Besides the fact that this latter result is in agreement with the proposed reverse learning theory of REM sleep function (Crick & Mitchison, 1983), it helps to formulate the contours of a new theory, claiming that sleep works for the calibration of neuronal excitability to a genetically determined baseline (Hansson, 2019).

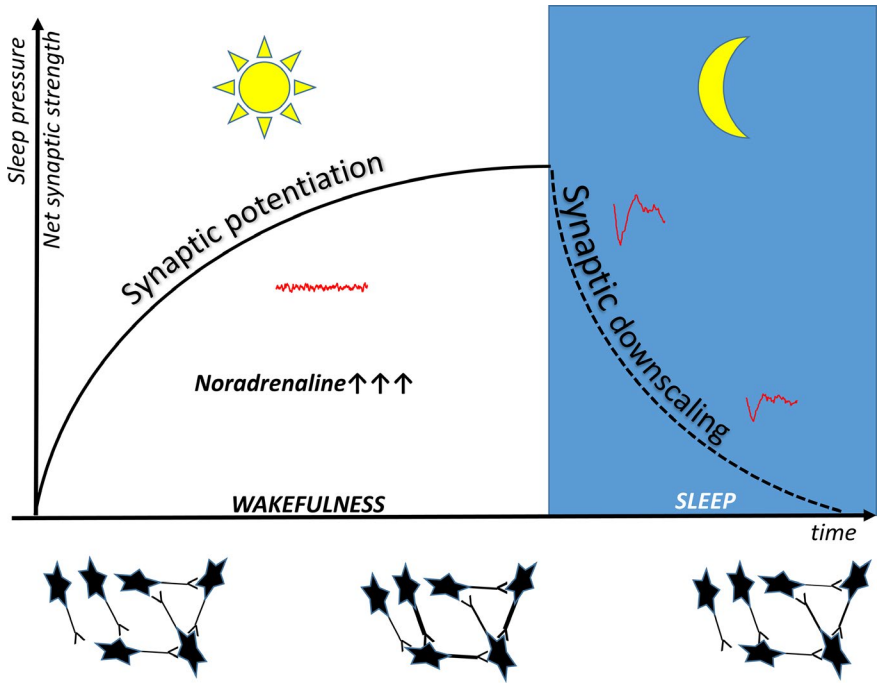

FIGURE 2 The synaptic homeostasis hypothesis of sleep (Tononi & Cirelli, 2014). Wakefulness is characterized by a high level of noradrenaline release and high-frequency, low-amplitude (desynchronized) electroencephalogram activity (red). As a consequence, the net synaptic strength is constantly increased, synapses are potentiated and sleep pressure increases, which is a reflection of increased net synaptic strength. During sleep, low-frequency oscillations (red) are associated with decreased noradrenaline release and a consequent decrease in net synaptic strength, reflected in decreasing sleep depth (reduction of the amplitude of slow waves)

8 | SLEEP AND ITS IMMUNOLOGICAL ASPECTS/FUNCTIONS

There are several tight links between sleep and immunity. Muramyl peptides are components of a sleep-inducing factor isolated from human urine and were found to be present in the cell walls of bacteria (Krueger, Pappenheirner, & Karnovsky, 1982). The muramyl peptides were shown to induce sleep by facilitating the release of several cytokines, including interleukin 1 beta and tumor necrosis factor alpha. The two immunological agents are indeed (local) sleep-inducing cytokines, thus termed somnogenic cytokines (Krueger & Opp, 2016; Pabst, Beranova-Giorgianni, & Krueger, 1999).

Long-term total sleep deprivation in laboratory animals (rats) induces a systemic bacterial invasion; that is, a breakdown in immune functions (Everson & Toth, 2000). Thus, not only is sleep induced/increased by ongoing immune challenge, but also sleep aids immunity. The latter point is supported by several recent findings indicating amongst others that postvaccination sleep increases immune competence as compared to postvaccination wakefulness (Lange, Dimitrov, Bollinger, Diekelmann, & Born, 2011). In addition, chronic sleep restriction is associated with chronic low-grade inflammation (Besedovsky, Lange, & Haack, 2019). There are hints that sleep aids the immune system by providing an optimal endocrine milieu for an adaptive immunological system consolidation in a manner that is seen in the case of neurally coded memories.

9 | SCEPTICISM REGARDING THE FUNCTION(S) OF SLEEP

Several authors cast doubt on the scientific reliability of the idea of searching for a specific function of sleep. Reasons for such scepticism are twofold. First of all, some researchers consider the evolution of sleep structure as a simple by-product of the evolution of wakefulness or other central nervous system structures and functions. As sleep structure (REM sleep percent and different EEG features) is a phenotype that is non-accessible in natural environments (i.e., without the intervention of sleep researchers), natural selection cannot act on such features. Natural selection acts on the phenomenological features of wakefulness, whereas the changes during the rest period are hypothesized to be consequences of such changes. Thus, the trivial function of sleep is considered to be rest and nothing more (Rial et al., 2007). Without a complete negation of the overall reasoning line behind this theory, it is worth mentioning that some aspects of sleep are maintained even in extreme ecological circumstances. Unihemispheric slow-wave sleep in aquatic mammals and migrating birds is a good example of the indispensable role of slow waves in these animals. However, one could consider slow waves as separate evolutionary inventions, which are not the core of sleep per se (Davis, Clinton, Jewett, Zielinski, & Krueger, 2011); slow waves could indeed be tightly associated with behavioural sleep in most, but not all animals (e.g., see the relatively frequent cases of sleep-walking in humans as well as the subjective sleep experiences in extreme conditions, such as the long marches of soldiers). Additional works (cited below) suggest that there are specific neurophysiological mechanisms favoured by, but not exclusive to, sleep, which are indeed involved in memory consolidation. Exemplary reports are revealing the facilitation of memory consolidation by brief periods of eyes-closed rest (Humiston & Wamsley, 2018), as well as the positive correlation of EEG slow oscillatory activity (<1 Hz) and mind wandering/decreased attention with memory consolidation during eyes-closed rest (Brokaw et al., 2016). In this case, we could talk about the function of slow waves or states characterized by low attentional investment but not sleep per se (see also section 10.1 below).

The second reason for scepticism in searching for a function of sleep is based on the state principle. NREM and REM sleep are behavioural states of the organism, very much like wakefulness is. But, is there a specific function of wakefulness? There is no other than the aid of the overall survival of the organism and a successful reproduction, which is far from being specific. Why are we searching for a function of (NREM or REM) sleep then? When we reflect on this last reasoning, one can argue that sleep states are regular co-occurrences of several psychophysiological phenomena (e.g., slow waves, sleep spindles, lowered heart rate in NREM sleep, sawtooth waves, rhythmic hippocampal slow activity, eye movement, and irregular breathing in REM sleep). The complexity of these co-occurring events might serve some function, as a complex system is much more than the sum of its elements.

10 | WHAT CAN BE CONSIDERED A FUNCTION OF SLEEP?

10.1 | Dose–response functions of sleep and physiological indexes

A proposed function of sleep should be directly associated with:

- The time spent in (the specific) sleep state (e.g., less sleep impairs glucose tolerance; Morselli, Leproult, Balbo, & Spiegel, 2010, or performance in vigilance tasks; Van Dongen, Maislin, Mullington, & Dinges, 2003).
- The mechanism/physiological features and processes of sleep (e.g., hippocampal sharp-wave ripple complexes during sleep are related to the sleep-dependent maintenance/consolidation of memory traces; Buzsáki, 1998).

Regarding the first point, there are very few attempts to calculate a dose–response function of sleep in relation to its physiological and behavioural consequences. A notable exception is the sleep restriction-induced decrease in vigilance and cognitive performance of human subjects. Performance lapses are indeed linearly related to the cumulative duration of wakefulness in excess of 15.84 hr (Van Dongen et al., 2003). However, several proposed functions of sleep

were never deliberately tested in this way. For example, sleep-related memory consolidation (or offline performance gains in procedural memory tasks) was observed after a whole night of sleep and a short daytime nap as well (Lahl, Wispel, Willigens, & Pietrowsky, 2008; Mednick, Nakayama, & Stickgold, 2003). Thus, it is important to note that this crucial aspect should be considered when evaluating a theoretical proposal regarding the functions of sleep.

A strong functional hypothesis would predict a complete deterioration of the function during prolonged periods characterized by the complete lack of sleep. A weak functional hypothesis predicts a decrease in that function, but not a complete deterioration of it. For example, hippocampal sharp-wave ripple complexes are seen during NREM sleep, but also during rest in rats (Buzsáki, 1986). Thus, the lack of sleep would decrease, but not eliminate completely, the function attributed to hippocampal sharp-wave ripple complexes (memory consolidation). Although this is a theoretically and empirically important point, many theories on the functions of sleep are not explicit in this regard. Another example of this type of research is related to sleep homeostasis, which was considered to be indexed by slow waves of sleep (sleep intensity), but not just the time spent in sleep (Borbély, 1982). Thus, more slow-wave activity during sleep has to be more efficient than a lower amount of slow-wave activity in a sleep period of equal length. Such findings are common and the relationship between sleep slow-wave activity and its proposed functions was quantitatively addressed in the literature in terms of glucose tolerance (Herzog et al., 2013), behavioural measures (Walsh et al., 2010), and so forth. However, local slow waves might emerge on a background of behavioural wakefulness (Vyazovskiy et al., 2011), whereas such local slow waves are not easy to embed into the models.

10.2 | Theories on the functions of sleep versus models of sleep regulation

Sleep regulation models aim to reproduce sleep behaviour and physiology as functions of other variables—for example, time spent in wakefulness (Borbély, 1982), time of day (Borbély, 1982), hypothesized firing rates of aminergic and cholinergic neurons in specific brainstem nuclei (McCarley & Hobson, 1974), and net increase in synaptic strength during wakefulness (Tononi & Cirelli, 2003). Some models of sleep regulation are not implying a specific function of sleep, whereas others are explicit in this regard. The former models, such as the two-process model of sleep regulation (Borbély, 1982) or the reciprocal interaction hypothesis of NREM–REM sleep alternation (McCarley & Hobson, 1974), are compatible with multiple functional hypotheses, whereas the latter can be considered as a specific theory on the function of sleep. An example of a sleep-regulation model that is implicitly a theory of sleep function is the hypnotoxin theory (Piéron, 1913) addressing sleep regulation (the accumulation of a toxin during wakefulness is the key factor of regulation), inherently proposing a functional hypothesis for sleep behaviour (removing the hypnotoxin from the central nervous system). Likewise, the synaptic homeostasis hypothesis (Tononi & Cirelli, 2003, 2014) considers net synaptic strength as a key factor in sleep homeostasis (a model of sleep regulation), but also implies a function for sleep: the downscaling of synapses. Given these partial overlaps, the present chapter addresses some, but not all, sleep-regulation models, which are currently cited in the literature and considered as leading theoretical frameworks in understanding sleep behaviour.

11 | SOME BASIC METHODOLOGICAL APPROACHES FOR TESTING THE FUNCTIONS OF SLEEP

11.1 | Sleep deprivation

Depriving subjects of sleep or some parts of it (e.g., REM sleep deprivation) is hypothesized to unravel its functions, by the measurable/visible and emerging (negative) somatic, vegetative and/or psychological consequences of sleep loss. The advantage of this approach is its apparent simplicity and ecological validity (many of us suffer partial sleep deprivation during our common everyday life; Abrams, 2015), whereas the drawback of it relies on several non-specific factors associated with sleep deprivation (stressful procedure, lack of rest associated with lack of sleep, etc.). Examples of this approach are the sleep deprivation-induced reductions in immune functions (Besedovsky et al., 2019) or the sleep loss-provoked impairments in hippocampal neural plasticity and neurogenesis (Kreutzmann, Havekes, Abel, & Meerlo, 2015). Long-term sleep deprivation is fatal in experimental animals (Everson & Toth, 2000), whereas a few days of total sleep loss were shown to have drastic, albeit reversible, effects in human subjects (see further details in Chapter A. 6. Effects of acute and chronic sleep deprivation). It has to be noted that the sleep-deprivation paradigm relies on the assumption that sleep is a whole-body process (i.e., the subject of sleep is the organism). However, both animal and human data indicate that sleep can be and is indeed at least in part local, thus prolonged sleep deprivation could be associated with increasing episodes of local sleep in specific networks or neuronal groups (Vyazovskiy et al., 2011). That is, even if sleep deprivation is natural, it is far from being an experimentally well-controllable situation. Another critique of the sleep-deprivation paradigm addresses the long-term deprivation procedures in experimental animals aiming to reveal the functions of sleep. It was argued that these interventions are of course extremely stressful and the resulting symptoms of experimental animals resemble the multi-organ failure syndrome, instead of a specific total sleep deprivation syndrome indicating the function of sleep (Rial et al., 2007).

11.2 | Experimentally altered sleep

Sleep is not deprived in this type of paradigm, but it is altered by drugs (suppressing cortisol release during late sleep, changes in the amount and intensity of EEG slow waves and spindles, and REM sleep reduction; Kaestner et al., 2013; Rasch et al., 2008;

Wagner et al., 2005; Walsh et al., 2010), sensory stimulation (slow wave or REM sleep disruption, or alternatively, rhythmic stimulation-induced increase in slow waves; Herzog et al., 2013; Ong et al., 2018), electrical stimulation (Marshall et al., 2006), and so forth. Altered sleep composition is followed by altered wake-time body functions or psychological processes, which are assumed to reflect the functions of sleep. An example of this approach is the electrical stimulation of the hippocampal formation in contingence with sharp-wave ripple complexes. The aforementioned stimulation induces a decrease in memory consolidation in rats, whereas the electrical stimuli, which left the sharp-wave ripple complexes unaltered, left memory consolidation intact (Girardeau et al., 2009). The decreased stress as compared to sleep deprivation is an advantage of this paradigm. In addition, more or less specific sleep processes and features are targeted by the intervention, which can lead to specific functional hypotheses. However, the interventions might induce non-sleep-related effects as well. Side effects and adverse events associated with pharmacological treatments, state-independent neurochemical changes induced by drug intake, as well as overall stress induced by sleep-disruptive sensory stimulation are examples of the above-mentioned potential non-sleep-related effects. Thus, it is not always easy to assess the sleep-specific outcomes of the studies.

11.3 | Experimentally altered wakefulness

Changes in wakefulness are followed by changes in sleep. These changes are assumed to indicate the functions of sleep. For example, intense cognitive activity is followed by changes in sleep (Cerasuolo, Conte, Giganti, & Ficca, 2020). Learning-induced changes in sleep spindles were hypothesized to reflect the functional role of sleep spindles in learning or memory consolidation (Morin et al., 2008). The advantages of targeting wakefulness instead of sleep are the intact sleep–wake cycles (no sleep deprivation) and the high ecological validity. Disadvantages of this latter approach are related to the non-specific aspects of wakeful interventions, which are not easy to assess (e.g., learning-associated stress). In addition, it is difficult to challenge the sleep system at an appropriate level in experimental settings (although field studies conducted during periods of intense second language learning are ideal for such challenges).

11.4 | Analysing interindividual differences

This non-interventional approach relies on the thesis that sleep features are correlated with habitual activities, individual specific physiological traits, genetic composition, and so forth. The correlation of these two factors can be considered to hint at the functions of sleep. For example, no associations between interindividual differences in sleep parameters and episodic memory consolidation were found, which "lead to the question whether sleep in general is important for memory consolidation but not so much the various sleep stages per se" (Ackermann, Hartmann, Papassotiropoulos, de Quervain, & Rasch, 2015). An advantage of this procedure is the lack of stress and the low-level ethical risks. Disadvantages are non-specificity and non-causality, as third (independent, but non-visible) factors might be involved in the correlations.

11.5 | The before versus after sleep approach

Functions of sleep are being tracked by comparing presleep and postsleep wakefulness in terms of some physiological variables. A good example is glucose uptake of the brain, which is decreased after a period of sleep, suggesting that sleep is involved in desaturation of energy needs of the central nervous system (Vyazovskiy, Cirelli, Tononi, & Tobler, 2008). Sleep-independent circadian variations in psychophysiological processes are not easily accounted for by this approach, but again: low risks and low levels of stress are advantageous features of this paradigm.

11.6 | Ontogenetic studies

Sleep composition and physiology change significantly during the human lifespan. These changes are considered as indexes of changing physiological needs. For example, periods of intense brain maturation are associated with a high proportion of REM sleep, thus REM sleep is hypothesized to be causally involved in maturation by providing periods of internal stimulation of neural networks (Roffwarg, Muzio, & Dement, 1966). Later stages of neuronal central nervous system development (between 2 and 20 years of age) are strikingly paralleled by the changes in the topography of sleep slow-wave activity, indicating that maximum slow-wave activity is providing the optimal physiological condition for developmental plasticity of brain networks (Kurth et al., 2012).

11.7 | Phylogenetic studies

Sleep timing, structure, and composition differ amongst species (Siegel, 2009). Nocturnal species sleep during the day (e.g., the rat), whereas diurnal species (e. g., humans) sleep at night. Crepuscular animals tend to be active around the transitional periods, whereas arrhythmic ones show no evident circadian patterns. The length of ultradian (NREM–REM) sleep cycles differs significantly amongst species and is positively correlated with body/brain size. Altricial mammals are characterized by longer REM periods than precocial ones. Differences in sleep are related to several factors, such as body size, brain size, metabolic rate, ecological variables (e.g., safe sleeping places, and predation risk), homeothermy, encephalization quotient, and altriciality. Correlations between sleep and non-sleep-related variables are hypothesized to indicate the functions of sleep (Anafi et al., 2019). Examples are the large amplitude sleep slow waves in different animal classes: although present in cerebral sleep records of some reptiles (Shein-Idelson, Ondracek, Liaw, Reiter,

& Laurent, 2016), large amplitude EEG slow waves were primarily found in mammals and birds during sleep. The difference between these classes is palliopallial connectivity (which is high in mammals and birds and low in other classes). Thus, "palliopallial connections that give rise to slow waves might also depend on slow waves to maintain their efficacy" (Rattenborg, 2006). The above-presented comparative approach is a viable method for unravelling the functions of sleep, although it is far from being ideal. An example of such problems is the comparativity of polygraphic sleep criteria. There is no universal physiological indicator of sleep, thus different species are characterized by (slightly or seriously) different indexes. How can we and how should we treat these differences? Are electrographically measured spikes reptilian spikes reflecting the hippocampal sharp-wave ripple complexes of mammalian rest and NREM sleep, or are they indicators of PGO spikes of mammalian REM sleep instead? There is no really unequivocal answer to such questions (Nicolau et al., 2000).

11.8 | Interim summary of methodological issues

As is evident from the above list of methodological approaches, no specific approach is ideal for unravelling the functions of sleep. Each of the approaches suffers from serious drawbacks, but each has specific advantages when compared to others. It is of utmost importance to note that well-elaborated theories on the functions of sleep are only rarely based on just one type of evidence. Thus, the approaches that were presented above are used in combination when studying the functions of sleep. In addition, the above list only refers to the typical methods and approaches. Other types of evidence might be cited and used in the literature.

12 | SUMMARY AND OUTLOOK

Sleep is more than rest, in a manner which is very obviously seen in the case of breathing, vocalization, and verbal functions. The circadian rhythm-driven periods of rest are superimposed by and used for much more complex, multilevel offline functions, pretty much like breathing supports vocalization and verbal behaviour (Włodarczak & Heldner, 2017). It is evident that sleep is a multilevel system, fulfilling a hierarchy of functions ranging from basic physiological needs (energy homeostasis, detoxification, appropriate timing of behaviour) to complex network-like functions (immune system, learning, neural network maintenance). If this concept is correct, there is no really ultimate function of sleep, but there are older and newer ones in phylogenetic terms. Such views have already been expressed in the literature (Krueger et al., 2008) and should be more thoroughly considered in the future.

CONFLICT OF INTEREST

The author declares no conflict of interest.

AUTHOR CONTRIBUTIONS

RB is the sole author who contributed to this manuscript.

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