Sleep, recovery, and metaregulation: explaining the benefits of sleep

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Abstract: A commonly held view is that extended wakefulness is causal for a broad spectrum of deleterious effects at molecular, cellular, network, physiological, psychological, and behavioral levels. Consequently, it is often presumed that sleep plays an active role in providing renormalization of the changes incurred during preceding waking. Not surprisingly, unequivocal empirical evidence supporting such a simple bi-directional interaction between waking and sleep is often limited or controversial. One difficulty is that, invariably, a constellation of many intricately interrelated factors, including the time of day, specific activities or behaviors during preceding waking, metabolic status and stress are present at the time of measurement, shaping the overall effect observed. In addition to this, although insufficient or disrupted sleep is thought to prevent efficient recovery of specific physiological variables, it is also often difficult to attribute specific changes to the lack of sleep proper. Furthermore, sleep is a complex phenomenon characterized by a multitude of processes, whose unique and distinct contributions to the purported functions of sleep are difficult to determine, because they are interrelated. Intensive research effort over the last decades has greatly progressed current understanding of the cellular and physiological processes underlying the regulation of vigilance states. Notably, it also highlighted the infinite complexity within both waking and sleep, and revealed a number of fundamental conceptual and technical obstacles that need to be overcome in order to fully understand these processes. A promising approach could be to view sleep not as an entity, which has specific function(s) and is subject to direct regulation, but as a manifestation of the process of metaregulation, which enables efficient moment-to-moment integration between internal and external factors, preceding history and current homeostatic needs.

Keywords: sleep, wakefulness, sleep homeostasis, sleep regulation, exercise, EEG

Introduction
Sleep is a universal behavior occupying a significant fraction of the 24-hour day, but its regulation and function(s) are far from being understood. There is an extensive amount of data and many theories, which suggest that sleep plays an active role in processes such as synaptic plasticity and memory functions, emotional regulation, metabolic functions and energy balance, macromolecule biosynthesis, removal of toxic substances and metabolic waste, or prophylactic cellular maintenance. Currently, none of these theories are generally accepted and some of them show considerable overlap. More recently, there has been a shift toward a novel view, which postulates that the beneficial role of sleep is related to it being a default state of the organism or cerebral networks or a state of adaptive inactivity. This view helps to explain the wide variability in the amount and architecture of sleep delay.
sleep between species, which can be accounted for by specific ecological factors including a difference in time needed to fulfill waking activities, such as feeding or reproduction.

One widely held view is that the need for sleep increases as a function of time spent awake, and that sleep is necessary to provide restoration with respect to molecular, cellular, or network changes, which occur specifically during preceding waking. This view is based on the notion that sleep is a regulated process, where several factors such as time of day, preceding waking duration, or specific types of activity are important determinants of the duration and intensity of sleep. A key observation is that the effects of various factors, acting at a specific moment of time (eg, ambient temperature) and reflecting preceding history, are revealed during specific changes in sleep and can be interpreted in terms of their involvement in sleep regulation. However, an alternative interpretation is that the essential characteristics of sleep, such as specific brain oscillations and the timing or duration of sleep, merely reflect other processes taking place at the time of measurement. The theoretical concept of metaplasticity is useful in aiding this discussion. Metaplasticity is considered as a higher-order form of plasticity and refers to the process that regulates the induction of plastic changes. For example, preceding history of activity, the levels of neuromodulators, ongoing synaptic state, or the global synaptic weight of the entire network are powerful modulators of the magnitude and direction of plasticity occurring at the level of individual synapses. In analogy with this concept, rather than considering sleep as a primary target of regulatory processes, it can be viewed as a process of metaregulation, that is a higher-order form of regulation, which accommodates a broad range of molecular, cellular and network processes altogether providing optimal (adaptive) wakefulness.

We define adaptive waking as a condition whereby the organism interacts effectively with the environment and is capable of maintaining normal physiological waking functions within strict physiological limits, which altogether increases chances of survival and successful reproduction. It should be pointed out that the terms “waking” and “sleep” did not originally have a scientific connotation, but were rather concepts defined qualitatively (for example, when referring to the absence of movement or a body posture), or based on the analysis of subjective experience. Nevertheless, this terminology persists today and is widely used in scientific literature, despite the terms often being too restrictive or inadequate for specific cases. It is worth noting that wakefulness, and in particular adaptive waking (as defined above), is a highly heterogeneous phenomenon. In simplistic terms, different types of waking can be classified based on the amount and character of movement or specific kinds of behavior. It is germane for this discussion, therefore, to introduce further subdivisions of waking, specifically into “low cost” and “high cost” elements, both with respect to energy and resources required for specific behaviors, and to their effects on future states. On the other hand, it is important to keep in mind that “sleep” is also an infinitely complex phenomenon, characterized by many interrelated processes. Some of these are relatively sleep specific, such as sleep oscillations or hormonal changes, while others are rather secondary processes and reflect the absence of sensory input and active locomotion, or physiological changes typical to a specific circadian time. As is the case for many other biological processes, the amount and dynamics of both waking and sleep are flexible, which is manifested on one hand as a considerable interindividual and interspecies variability, and on the other hand, in the capacity to stay awake beyond habitual sleep time, which can be modulated by involvement in specific behaviors, feeding and environmental changes such as ambient temperature and light.

The central theme to this article is that given a complex interdependency between physiological, behavioral, and psychological variables, as well as the unique effects of preceding and current state, it is difficult to estimate the pure effect of sleep or a lack thereof on any specific variable. For example, at the molecular level, mistimed sleep or sleep deprivation (SD) is associated with an altered transcription or translation of a wide range of molecules, which are implicated in core circadian rhythms generation both centrally and in the periphery, and are also involved in a wide range of other fundamental physiological processes. At the neuroanatomical level, circuits involved in energy homeostasis, waking, and sleep also show a considerable overlap, suggesting intimate links between them. At the behavioral level, effects of SD or preceding sleep on cognitive functions or psychomotor vigilance may be influenced by motivation or state instability.

In this article, first, the defining characteristics of sleep will be briefly considered. Then, some of the existing evidence for a role of sleep in recovery processes will be discussed, focusing on specific sleep-related phenomena such as the homeostatic regulation of sleep, the response to physical activities and the beneficial effects of sleep on subjective and objective measures of waking and performance. Finally, the concepts of recovery sleep and sleep regulation will be critically discussed.
What is it like to be asleep?

Sleep is traditionally defined as a behavioral state that encompasses several essential characteristics used as defining markers, such as immobility or reduced behavioral responsiveness to external stimuli. Although these features are common across humans and animal species, a critical analysis reveals that they are often neither sufficient nor necessary for the classification of sleep, and their relevance for sleep regulation is not clear.

With regard to the absence of locomotor activity and voluntary movement, the question arises whether it is a necessary prerequisite or a consequence of a sleeping state, or both. One possibility is that immobility is necessary to prevent the flow of sensory information from proprioceptors, such as Golgi tendon organ or muscle spindles, to higher-order brain regions, which could otherwise interfere with ongoing spontaneous sleep activity. This is supported by recent evidence, which suggests that movement is associated with membrane depolarization in the neocortex, while stimulation of the motor cortex during anesthesia affects sleep-like patterns of activity even in distant cortical regions. Alternatively, it is possible that cerebral activity during sleep, characterized by regular cessations of spiking and synaptic activity across widely-distributed brain areas, effectively disrupts large-scale network processing which is necessary for initiating and generating complex voluntary movements. Indeed, most of the brain is known to be involved to some extent in aspects of movement such as sensorimotor coordination, movement planning, and execution, which entail offline emulation of the body and the environment, required for efficient solving of various kinematic and dynamic tasks. Yet another possibility is that reduced locomotion during sleep is merely a consequence of reduced activity of those subcortical neuromodulatory areas, which are implicated both in maintaining arousal or other waking functions and necessary for movement, but can be, at least in part, dissociated from the sleeping state itself. In summary, while the absence of movement correlates with the occurrence of sleep, its relevance remains uncertain and further criteria are necessary for defining sleep.

Along the same line, disconnection from the sensory world may also be both a cause and a consequence of the sleeping state. An early study suggested that individual neurons may transition into “sleep-like” activity, despite the animal continuing to respond to stimuli. More recently, it was found that cortical neurons in the auditory cortex maintain responsiveness to auditory stimuli of various characteristics and modality while the animal remains asleep, unless the stimulus intensity is too high, when a startle response can trigger an arousal. This study led the authors to hypothesize that while primary sensory areas may be still responsive, the propagation of the stimulus to higher-order brain areas required for a global awakening is prevented by ongoing neuronal activity. This hypothesis is supported by the evidence that electrical microstimulation of a local cortical area during spontaneous non-rapid eye movement (NREM) sleep in rats elicits a stronger or attenuated response depending on background activity in the target area. Subcortical neuromodulatory areas proposed to be essential for global state transitions and information processing have also been shown to have increased activity close to an arousal. However, hypocretin neurons also may increase firing in response to auditory stimuli even when the animal remains asleep. This therefore suggests that both primary sensory cortical areas and subcortical regions are involved in monitoring the environment, but other factors are essential for triggering a global behavioral arousal. Moreover, optogenetic stimulation of hypocretin neurons did not necessarily lead to an immediate awakening, but rather increased the probability of an arousal in the next minute and prolonged the latency to sleep, especially during deep sleep. Thus, although sensory disconnection is an essential characteristic of sleep, it appears that the sleeping brain remains active in processing sensory information, and may even have capacity to extract task-related information, which indicates the presence of covert higher-order cognitive processing.

As is well known, there is a considerable overlap between neurotransmitter systems involved in maintaining behavioral arousal, sensory responsiveness, and locomotion. These are used as defining characteristics for wakefulness, but are also crucial for such higher-order waking functions as neurobehavioral performance, attention, and cognition, which are affected to some extent by prolonged waking or by the time of day. An essential process in the initiation of sleep is a decreased activity in subcortical “wake-promoting” nuclei, which leads to characteristic changes in the electroencephalogram (EEG) and neuronal and activity in the forebrain. The occurrence of EEG slow waves is an essential defining characteristic of physiological NREM sleep, the polysomnogram detection of which is dictated by the amplitude and frequency of these slow waves, in addition to other electrographic phenomena such as spindles. However, as has been acknowledged by many, slow waves and their underlying cellular and network counterpart – the slow oscillation – can be dissociated from physiological NREM sleep. For example, sleep-like activity has been recorded in brain slices in vitro, under anesthesia, in isolated...
cortical slabs, during local application of norepinephrine antagonists, and during quiet waking. Moreover, slow waves during sleep can be reliably induced by electrical, auditory, or transcranial magnetic stimulation or by sensory inputs from periphery. An interesting observation is that sleep has features of a “default state”, such that neuronal cultures or isolated cortical slabs spontaneously generate patterns of activity similar in some respects to cortical activity during physiological sleep. Notably, although it is sometimes questioned whether cortical EEG slow-wave activity (SWA, EEG power below 4 Hz) is essential for sleep or sleep regulation, it remains a key measure for defining sleep in experiments where subcortical systems are targeted.

The lack of progress in establishing direct links between states of vigilance, overt behaviors, and specific EEG activities has been acknowledged for some time. Important insights can be obtained from focusing on specific phenomena characterizing waking and sleep such as their architecture, spatio-temporal dynamics of brain activity, as well as their regulation. More recently, it has been proposed that homeostatic regulation of sleep is its essential feature. It can be argued that while EEG slow waves per se may merely reflect a specific network state, the amount of excitatory input, and lowered levels of arousal-promoting neuromodulators typical for quiet wakefulness and immobility, their homeostatic regulation suggests an additional functional aspect, which allows to distinguish sleep from other conditions.

**Homeostatic regulation of sleep and EEG SWA**

Homeostatic regulation of sleep refers to the capacity to sleep longer or more intensely to compensate for sleep deficit. According to its original formulation, the homeostatic principle can be summarized as “the longer is the period of waking, the deeper or longer is subsequent sleep”. SD is one of the main tools used to assess the integrity of homeostatic sleep regulation mechanisms in both animals and humans. Early studies utilizing SD or chronic sleep curtailment protocols reported consistent effects of SD on specific sleep stages. In one early study, young male subjects, who slept only 3 hours per day for eight consecutive days showed increased stage 4 sleep during sleep opportunity periods, and these results were corroborated by another follow-up human study. Likewise, in dogs, 12-hour forced wakefulness led to an increase in delta wave sleep during the first half of the night. In a quantitative EEG study, delta band power density was found to be significantly higher after SD compared with baseline for total sleep time as well as for sleep stages 2, 3, and 4. Notably, and consistent with many follow-up studies, the effects observed were not restricted to the traditional delta band, but also extended into higher frequencies. Importantly, while the levels of SWA are invariably higher after SD, it has been shown that even relatively short periods of spontaneous waking lead to a predictable progressive increase in subsequent SWA, which led to the notion that it is a sensitive measure of sleep intensity. Interestingly, the amount of sleep or the levels of SWA before 6-hour SD affect the initial recovery sleep after SD, suggesting that sleep history leaves a trace, which is long lasting and resistant to erasure.

Notably, apart from the well-known overall decline of spectral power in the slow-wave frequency range with decreasing sleep pressure, there is also a redistribution of power toward lower frequencies, resulting in a shift in the spectral peak. As a consequence, several studies have reported a dissociation between the time course of EEG power in frequencies <1 Hz and the remaining frequencies within the slow-wave range. More recently, it has been proposed that homeostatic regulation of sleep is its essential feature. It can be argued that while EEG slow waves per se may merely reflect a specific network state, the amount of excitatory input, and lowered levels of arousal-promoting neuromodulators typical for quiet wakefulness and immobility, their homeostatic regulation suggests an additional functional aspect, which allows to distinguish sleep from other conditions.
need, including the regulation of brain metabolism, activity-dependent release of cytokines, and synaptic plasticity. The compensatory increase in SWA after a period of waking in proportion to its duration and the decline of SWA after sleep have been considered correlates of a “recovery” process occurring during sleep. The proposed changes requiring renormalization are diverse and span from energy homeostasis and removal of toxic products of metabolism to membrane repair and macromolecules biosynthesis. However, whether these recovery processes are actually taking place and what exactly is being recovered during sleep is still a matter of debate and will be considered next.

**Sleep need, sleep debt, and recovery sleep**

Sleep need, sleep debt, and recovery sleep are widely used concepts, in both scientific literature and beyond. Searches on these and related phrases return many hundreds citations in PubMed and countless web pages. “Recovery” is usually defined as regaining something that has been lost or taken away, or to restore or return to any former (better) state or condition. It is often concluded or implied that at least one of the functions of sleep is to provide recovery, and that the need to sleep or sleep debt reflects the need to obtain sufficient recovery. In addition, recovery is mentioned frequently when referring to a “compensatory” increase (rebound) in sleep time or sleep intensity after SD. Surprisingly, the literature demonstrating unequivocal evidence for recovery which can be attributed exclusively to sleep is scarce if not non-existent — the aspect that is rarely considered critically. Consistently, the role of sleep with respect to a specific variable is often inferred from the changes observed in the absence of sleep. However, the effects seen in conditions of insufficient sleep may rather reflect regulatory processes or a manifestation of a drive to initiate sleep rather than consequences of the lack of sleep itself. Arguably, SD is a replacement of sleep with other behaviors or states, rather than merely its absence. For example, if specific circuits requiring “recovery” enter sleep-like states after a certain amount of activity, the altered network dynamics would likely affect a variety of centrally-regulated functions, which would manifest itself at the level of behavior or metabolic disturbances. However, it does not necessarily mean that sleep normally plays a role in restoring those changes.

On a more fundamental level, in order to rigorously assess the recovery role of sleep it is necessary to compare pre-sleep with post-sleep values, a process that involves multiple confounding factors that are difficult to disentangle from one another. Specifically, the initial pre-sleep value of the variable under scrutiny does not only reflect the current state at the moment of measurement, but is also determined by the combined effects of preceding waking duration and specific waking activities, which are in addition influenced by the circadian phase.

**Sleep and recovery after physical fatigue**

Since one of the main defining characteristics of sleep is the absence of movement, the question arises how and whether physical activity affects subsequent sleep. This question is also important since the compensatory rebound of sleep or sleep intensity after SD may depend on specific types of behavior, cognitive activities, or merely locomotor activity, which is often elevated when the animals or humans are sleep-deprived. Furthermore, it can be expected that sleep is beneficial for reversing tiredness typical after exercise. For these reasons, the role of sleep in recovery has been studied extensively in relation to exercise, both in animals and in humans.

Early studies suggested that sleep facilitates recovery of the fatigue acquired during exercise. In one of the first experiments, cats that were subjected to treadmill running were found to have compensatory sleep changes that manifested as a decrease in sleep latency and an increase in synchronized EEG activity. These data were supported by the observation that rats showed an increase in daily sleep time after SD by forced treadmill activity. The hypothesis that sleep is associated with physical fatigue was also tested in a study where several different regimens of exercise were studied in two human subjects. This study found a whole-night increase in slow-wave sleep (SWS) that was related to the amount of physical fatigue, while the amount of rapid eye movement (REM) sleep was reduced. These
results have since been confirmed in a more recent study, while another study found a consistent increase in SWA and stage 2 sleep, accompanied by a reduction in REM sleep in fit subjects across four conditions varying by the amount of exercise (running). However, a follow-up study from a different laboratory, in which eight subjects underwent either morning or evening exercise identified contradicting results. Specifically, while evening exercise resulted in an increase in stage 3 during subsequent sleep, morning training did not lead to any changes in sleep, which led the authors to conclude that recovery from muscle fatigue does not require sleep, and can instead be fulfilled during waking.

In rats, SD by forced locomotion on a “water wheel” resulted in an increased amplitude of the EEG recordings and intrusion of microsleeps during waking, while the subsequent sleep showed an increased level of high amplitude slow waves during NREM sleep. It is important to mention that it is unclear whether locomotor activity or waking duration per se accounts for this effect. In a control group, which had been awake for the same duration but walked much less, the rebound of sleep was similar, leading the authors to suggest that exercise per se has little influence on sleep. This notion was supported by a study showing that the effects of 12-hour SD by forced locomotion in rats were similar irrespective of wheel turning speed. It should be noted, however, that forced exercise may differ from voluntary exercise. In cats, it was found that more physical exercise was associated with a larger increase in SWS during subsequent sleep. It cannot be excluded that differences may be due to other factors such as the cognitive and motor effort needed to keep up with the rotation of the treadmill or even attempts to counteract the treadmill motion and accompanying stress associated with this. A similar conclusion has been reached in a human study where six men would march for 34 km each day with 5 hours rest allowed between the end of exercise and the subsequent sleep opportunity onset. The effects on subsequent sleep were variable between individuals however seemed to correlate with the levels of urinary 17-hydroxycorticosteroids. In another study, cycling for 3 hours also did not affect subsequent sleep. An interaction between exercise and SD was recently documented in a study where the exercise-related increase in growth hormone was elevated in sleep-deprived individuals.

A significant limitation of human studies is that obvious technical difficulties prevent artifact-free EEG recordings during running per se. It was suggested that exercise is closely linked to cognition and does not entail merely physical effort, and this may underlie beneficial effects of exercise on cognition in aging. Interestingly, in overweight adults, exercise led to a reduction in default mode network activity in the precuneus. Another recent study found that functional connectivity in the default mode network was increased following 6–12 months of training, which led the authors to suggest that it reflects experience-dependent plasticity, as it was associated with an improvement in executive function.

Notably, exercise appears to affect specific aspects of the compensatory sleep response. Specifically, in a rat study it was found that both EEG wave incidence and amplitude are responsive to prior wakefulness, but only incidence was influenced by prior exercise. This result is interesting given the different changes in network activity associated with specific parameters of EEG slow waves. Increased slow-wave incidence may suggest higher excitability or bistability of cortical networks, rather than increased network synchrony, which is associated with higher slow-wave amplitude as a result of longer and more profound population silence.

Rodent studies have also shown that access to running wheels can substantially affect the distribution, amount, and architecture of vigilance states and activity across 24 hours, as well as EEG SWA. Notably, frontal predominance of SWA was enhanced after a period of waking without running wheel activity leading the authors to hypothesize that more diverse waking behaviors and activity led to a higher need for local or global “recovery”. An intriguing observation was that when access to the wheel was not prevented, the duration of the first spontaneous waking period after dark onset was substantially extended compared with the wheel block condition. While this may suggest that in the absence of engaging activity the mice withdraw from active behaviors and therefore fall asleep earlier, it may also suggest that exploratory or diverse behaviors lead to a faster accumulation of sleep need as compared to stereotypical running behavior.

In summary, it is not surprising that variable and discrepant results have been obtained in studies addressing the effects of exercise on sleep, or assessing the “recovery” role of sleep after physical fatigue. It is likely that a simple relationship cannot be expected, as the effects of exercise may be strongly determined by the kind of exercise. This example highlights one of the difficulties in investigating global recovery functions of sleep. The next chapter will discuss briefly the role of sleep in central local mechanisms underlying behavioral performance.

**Does sleep recover behavioral performance and cognitive function?**

It has been argued that prolonged wakefulness leads to a progressive impairment of fundamental waking functions...
such as attention, learning, sensorimotor integration, and a range of executive cognitive functions.\textsuperscript{65,133,154} The mechanisms underlying the deleterious effects of insufficient or disrupted sleep are unclear and may be related to the lack of sleep (cumulative effects of preceding history) or merely reflect the tendency to enter sleep during the task (state dependency). By targeting relevant brain circuits in a selective way it is possible to investigate whether insufficient or disrupted sleep affects specific behaviors. Alternatively, cognitive and behavioral deficits may be secondary to a more fundamental global breakdown occurring at molecular, cellular, or network levels, which are incompatible with wakefulness in general.\textsuperscript{155}

There is extensive evidence for use or activity dependency of sleep at the level of specific neural circuits.\textsuperscript{156} These studies were triggered by an observation that during spontaneous sleep SWA is not uniform across the cortical surface, but shows topographic gradients. In both humans and animals, SWA is more intense in the frontal derivations, especially during early sleep or after SD.\textsuperscript{157–162} Such changes may arise from anatomical differences, but could also be related to differential activation of specific brain regions. Specifically, studies have shown that peripheral stimulation or spontaneous use of circumscribed cortical areas leads to more intense EEG slow waves localized to the corresponding cortical regions.\textsuperscript{163–165} In addition, local, topographically distinct enhancement of slow waves was associated with learning of a motor task,\textsuperscript{124,166,167} while unilateral arm-immobilization led to a local decrease in slow waves.\textsuperscript{168} While a substantial body of evidence has been accumulated showing local activity-dependent changes in sleep SWA, it is important to keep in mind that the effects are usually modest, rarely exceeding 10%–20%, and by far lower than global wake-dependent changes. Nevertheless, such observations suggest that waking activities could affect the intensity of subsequent sleep in a selective manner, and that local changes in sleep activities may provide localized restoration. Activity-dependent sleep theories have implied that specific waking activities may lead to a selective disruption at the level of specific brain circuits resulting in their deterioration.\textsuperscript{67,169} Unfortunately, while many studies report deleterious effects of SD on specific neurobehavioral and cognitive functions, relatively few specifically addressed whether sleep can reverse the observed changes, and whether the effects are truly sleep specific.

An early study used visual stimulation during waking to test the hypothesis that visual load during SD affects subsequent recovery sleep in human subjects.\textsuperscript{170} Following the condition of high visual load, a significant increase in stage 4 sleep during recovery nights was identified. In another study, a group of healthy subjects and insomniacs were subjected to 64-hour SD, and a decline in the performance measures based on reaction time and immediate recall in both groups was found, while subjective sleepiness increased.\textsuperscript{171} Notably, the behavioral variables were restored after 8 hours of sleep, although it took longer for sleepiness to renormalize. Recently, SWS disruption was found to primarily lead to an increase in sleepiness with only minor effects on other aspects of daytime functioning.\textsuperscript{172} PVT measures and sleepiness have been shown to recover at different rates following sleep restriction,\textsuperscript{173} where the amount of sleep during the recovery period was an essential variable.\textsuperscript{174} Somewhat different results have been obtained in a study, where after SD, subjective sleepiness nearly recovered to the baseline level on the first recovery day, but fatigue and performance in a high-order cognitive task took 2 days to return to baseline levels.\textsuperscript{175} This was supported by another study which reported that the negative effects of SD on task-switching performance were reversed by only one night of recovery sleep.\textsuperscript{176} Similarly, in another protocol where the durations of sleep and wake episodes were increased to 10 and 32.85 hours, respectively, to yield a reduced sleep-to-wake ratio of 1:3.3, sleep consistently restored vigilance task performance during the first several hours of wakefulness.\textsuperscript{177}

Interestingly, there is evidence that even short periods of sleep can be beneficial. Specifically, a short afternoon nap (<30 minutes) significantly reduced subjective sleepiness and fatigue in the afternoon both in elderly and in young subjects, while subjective mood and performance in a task were also improved.\textsuperscript{178,179} Nevertheless, it remains unclear whether the improvements or restoration observed after sleep reflects an active recovery process obtained during sleep, or a diminished drive to initiate sleep.

### What makes sleep after SD a “recovery sleep”?

Sleep after SD is usually enhanced, with respect to both its total duration and its intensity as measured with EEG SWA,\textsuperscript{96,141,180,181} although notable differences have been found between studies, species, genetic backgrounds, age, the time of day, environmental conditions, and the method used to perform SD.\textsuperscript{97,182–192} Moreover, substantial interindividual variability in the response to SD has also been found.\textsuperscript{35,66}

The terminology used to denote the response to SD would benefit from clarification and improvement. On the one hand, it can be argued that if sleep is necessary to provide recovery,
eg, if it compensates for preceding waking, then all sleep is “recovery sleep”, irrespective of the duration of previous waking. On the other hand, it cannot be excluded that deep intense sleep after SD may have higher “recovery” value, and recovery will be delayed under circumstances where this recovery is prevented, such as in selective slow-wave deprivation experiments, or when SWS is eliminated specifically during the first part of the night. Local use-dependent changes in SWA after selective peripheral stimulation have also been considered as evidence for a higher need of local “recovery”, although no causal experiments preventing local increases of SWA after peripheral stimulation have been performed to date.

There have been several attempts to manipulate SD protocols to investigate the subsequent recovery sleep. In one study, physostigmine was administered during SD to induce REM-like sleep in awake rats, while atropine was used to produce EEG slow waves typical of those found during NREM sleep. These manipulations did not substantially affect subsequent recovery sleep, and it was concluded that pharmacologically induced sleep-like patterns cannot substitute for physiological sleep. However, in another study, sleep characteristics after 6 hours of propofol anesthesia following SD were similar to undisturbed recovery sleep. A more recent study found that recovery sleep after isoflurane or desflurane anesthesia administered for 1 hour at the end of SD was similar to spontaneous sleep, suggesting that merely the presence of slow waves, or reduced neuronal activity may be sufficient to achieve at least initial recovery. The active role of slow waves in providing synaptic renormalization was suggested by the finding of a correlation between sleep intensity and changes in cortical evoked potentials across sleep. Typically, slow waves are absent during active waking, although in some cases a dissociation between behavior and cortical activity can be induced pharmacologically, such as by administration of muscimol or atropine. The role of pharmacologically induced slow waves in subsequent sleep is not entirely clear, mainly because it is often difficult to dissociate residual drug effects from the effects of altered preceding state. However, pharmacological “induction” of wakefulness led to an expected increase in sleep time and EEG SWA during subsequent sleep, which suggests that the dynamics of the underlying regulatory processes were not altered.

These findings are consistent with a relationship between brain activity during SD and subsequent sleep, although it should be noted that this relationship is often not straightforward. For example, an increased leakage of slow waves into waking EEG may discharge sleep pressure to some extent, or slow down the buildup of sleep pressure. The presence of “sleep-like” activity in an otherwise awake brain may however also merely be a reflection of a “sleep-deprived” state and indicate a tendency to initiate sleep, while by itself contributing little to the dissipation of sleep need. Recently, it has been proposed that the occurrence of sleep-like activities during waking is a manifestation of the process of prophylactic cellular maintenance. According to this hypothesis, and consistent with previous models, individual neurons and local networks tend to transition into a sleep-like state after a specific amount of activity, which may serve to re-allocate energy substrates essential for cellular maintenance processes. The occurrence of such sleep-like events would be expected to affect the entire network dynamics, and could precipitate other deficits. Alternatively, this activity may in theory permit extension of the time spent awake by performing “online” maintenance.

While there is considerable evidence that “recovery” sleep occurs as a result of or is related to preceding waking activities, some notable exceptions under both normal and pathological conditions are well documented. For example, individuals in a persistent vegetative state with greatly impoverished waking that may require little subsequent recovery sleep have been found to have partially preserved sleep-wake cycles. Evidence of increased SWA during the initial sleep after hibernation or torpor suggests that the mere absence of SWA and physiological sleep may be sufficient to necessitate recovery processes. Finally, it cannot be excluded that at least some of sleep’s functions may be performed in other states. For example, a recent study found that a period of meditation does not only temporarily restore behavioral performance, but may also lead to a reduced sleep time, suggesting that it may partially substitute for sleep.

**Sleep and metaregulation of physiological homeostasis**

In summary, while the notion that sleep proper is a regulated process remains an important concept, the existence of many factors that profoundly influence sleep, or more precisely, manifest themselves in specific sleep parameters, makes it hard to determine what exactly is being regulated. Likewise, the role of sleep in recovery remains one of the predominant hypotheses, despite existing evidence being insufficient and the likelihood that it will remain so due to several reasons.
Firstly, sleep is a complex process, making it difficult to dissect the contribution of specific phenomena or temporal and spatial aspects associated with sleep, to its recovery functions with respect to specific physiological variables. Secondly, any attempt to investigate the recovery role of sleep with respect to a specific variable must also take into account other essential factors, such as circadian phase, which are often difficult to disentangle. Further undoubtedly necessary efforts will likely bring important advances in our understanding of molecular and cellular processes that benefit from sleep. It is however essential to keep in mind that sleep (as it is traditionally defined) is ultimately a global behavioral phenomenon and that the beneficial effects of sleep are likely to be found at a higher-order level, rather than in specific independent variables.

An important consideration is that the characteristics currently employed to define sleep are mechanistically directly linked to cerebral activity, despite current debate as to whether sleep benefits and SD harms the body or the brain or both. It should be noted that in laboratory experiments SD is achieved by enforcing exploratory behavior or locomotion, using pharmacological means targeting wake-promoting neuromodulators, or by sensory or direct brain stimulation, thus targeting the brain in the first instance. Moreover, the success of SD is determined by monitoring EEG/EMG traces, body posture, and movement or by testing the responsiveness of the subject, ie, by readouts of cerebral activity, rather than by measuring peripheral functions. It is well known, however, that sleep is a major modulator of hormonal levels, metabolic status, and the immune system, while SD or sleep restriction are associated with a wide range of peripheral changes that may be visible, for example, at the level of the transcriptome or metabolome. However, unlike the neurophysiological effects of sleep and SD, the changes in the neuroendocrine, metabolic, or immune systems are less easily accessible to direct observation in real time, and therefore are not targeted specifically during SD procedures.

It has been proposed that the temporal organization of sleep and circadian rhythms enable the coordination of a wide range of cellular and metabolic processes, which together enable stability and survival. The question, however, remains whether and in fact how different processes interact to achieve homeostasis of specific variables at the cellular level to enable optimal adaptive wakefulness at the level of the whole organism. One possibility is that the regulation of specific physiological variables occurs relatively independently, but since the substrate (the organism) is shared purely additive interactions are observed. An alternative scenario is that rather than sharing the substrate, the key molecules or brain circuits are instead shared between specific functions, and a change in one of them would be accompanied by changes in another. Another possibility, which has not been considered previously, is that an additional level of regulation exists, which could take a form of a metaregulation. In economics, meta-regulation refers to a mode of oversight, where the regulatory agency induces self-regulatory arrangements at the lower levels, without interfering with the rules employed downstream. An essential aspect in this form of regulation is the ultimate goal that has to be set, which could be the maintenance of physiological homeostasis in general or adaptive wakefulness in particular. According to this view, sleep is not a distinct entity, which is regulated independently and has a specific function, but, at any given moment, represents the process of metaregulation, which reflects an interaction between internal and external factors, preceding history and current homeostatic needs.

This view describes well the role of sleep in enabling adaptive wakefulness without invoking its recovery (or any specific) function and has several theoretical implications. First and foremost, it accounts for sleep being a highly complex hierarchical process, consisting of at least several distinct sub-states, many processes, anatomical structures, and biochemical pathways involved, which share substrates, integrate environmental influences and preceding history, and interact in many ways. Secondly, if adaptive wakefulness, defined in terms of behavior, the probability of survival, and energy homeostasis is the ultimate target of the metaregulation process, then it would be expected that there are multiple ways to achieve it, which can account for inter-species variability and flexibility in characteristics of the states we call waking and sleep. Finally, the changes observed when sleep is insufficient or absent, such as metabolic disturbances or behavioral deficits, could be viewed not as negative consequences of sleep loss, but rather as manifestations of the breakdown of the process of metaregulation, which no longer provides adaptive wakefulness.

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Disclosure
The author reports no conflicts of interest in this work.

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