

Summary

Only the recording of brain electrical activity (electroencephalogram, EEG) during sleep revealed that sleep is an active process that is tightly regulated. Thus, every night we cycle through a seemingly predefined series of discrete states (NREM and REM sleep) each with its characteristic EEG activity pattern. Sleep need is also regulated and depends to a large extent on how long we stay awake. Moreover, the longer we stay awake the more intense sleep becomes. The quantitative analysis of the sleep EEG led to the discovery of slow-wave activity (EEG power below 4.5 Hz) as a marker of sleep intensity, which closely reflects the homeostatic regulation of sleep. A recent hypothesis about the function of sleep attributes a central role in the maintenance of cortical connections, i.e. synapses, to this major EEG characteristic of NREM sleep. According to the synaptic homeostasis hypothesis, NREM sleep rich of slow waves favours the cleaning or recalibration of cortical connections, making them more efficient for signal transduction. Such increased efficiency of synapses might be responsible for the widely observed sleep dependent performance improvements. The clinical impact of the synaptic homeostasis hypothesis is exemplified by a potential relationship between the increased seizure risk during deep NREM sleep and changes in cortical signal transduction.

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Key words: Electroencephalogram, slow waves, sleep homeostasis, synaptic plasticity

Funktionelle Aspekte des Schlaf-EEGs

Erst die Ableitung der elektrischen Hirnaktivität (Elektroenzephalogramm, EEG) während des Schlafes zeigte, dass der Schlaf ein aktiver, eng regulierter Prozess ist. So durchleben wir jede Nacht eine scheinbar vordefinierte Serie von diskreten Stadien (NREM- und REM- Schlaf), jedes mit seinem charakteristischen EEG-Aktivitätsmuster. Auch das Schlafbedürfnis ist reguliert und hängt grösstenteils von der vorgängigen Wachdauer ab. Ausserdem nimmt die Schlafintensität mit zunehmender Wachdauer zu. Die quantitative Analyse des Schlaf-EEGs führte zur Entdeckung der langsamwelligen Aktivität (EEG-Aktivität unter 4.5 Hz) als Marker der Schlafintensität, welche die homöostatische Regulation des Schlafes präzise reflektiert. Eine kürzlich

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postulierte Hypothese über die Funktion des Schlafes weist dieser langsamwelligen Aktivität eine zentrale Rolle in der Erhaltung kortikaler Verbindungen oder Synapsen zu. Die synaptische Homöostase-Hypothese besagt, dass NREM-Schlaf mit vielen langsamen Wellen verantwortlich für das „Säubern“ oder Kalibrieren von kortikalen Verbindungen ist. Dies führt zu einer Effizienzsteigerung der Signalübertragung, welche für die vielfach beobachtete schlafabhängige Leistungssteigerung verantwortlich sein könnte. Der klinische Einfluss der synaptischen Homöostase-Hypothese wird anhand des möglichen Zusammenhangs zwischen dem erhöhten Epilepsieanfallsrisiko im Tiefschlaf und Änderungen der kortikalen Signalübertragung dargestellt.

Schlüsselwörter: Elektroenzephalogramm, langsame Wellen, Schlafhomöostase, synaptische Plastizität

Aspects fonctionnels de l'EEG du sommeil

Il a fallu l'invention de l'électroencéphalogramme (EEG), donc la possibilité d'étudier les signaux électriques produits par le cerveau pendant le sommeil, pour prouver que le sommeil était un processus actif étroitement régulé. Ainsi, nous traversons chaque nuit une série de stades discret (sommeil NREM et REM) apparemment prédéfinis dont chacun présente un schéma d'activité EEG caractéristique. Le besoin de dormir est lui aussi régulé et dépend en grande partie de la durée de la phase d'éveil qui l'a précédé. De plus, l'intensité du sommeil croît à mesure que la phase d'éveil a été longue. L'analyse quantitative de l'EEG du sommeil a révélé l'activité à ondes lentes (activité EEG inférieure à 4.5 Hz) en tant que marqueur de l'intensité du sommeil qui reflète avec précision la régulation homéostatique du sommeil. Une hypothèse récemment postulée au sujet de la fonction du sommeil attribue à cette activité à ondes lentes un rôle central dans la conservation des liaisons corticales ou synapses. L'hypothèse de l'homéostasie synaptique postule que le sommeil NREM avec ses nombreuses ondes lentes est responsable de « l'épuration » ou du calibrage des liaisons corticales. Il en résulte une meilleure efficacité dans la transmission des signaux qui pourrait être responsable de l'augmentation de performance dépendante du sommeil souvent

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constatée. L'influence clinique de l'hypothèse de l'homéostasie synaptique est présentée à l'appui de la relation possible entre le risque accru de crises épileptiques en phase de sommeil profond et des modifications de la transmission de signaux corticaux.

Mots clés : électroencéphalogramme, ondes lentes, homéostasie du sommeil, plasticité synaptique

Introduction

For a long time it was believed that sleep is a passive process, whereby a brain deprived of sensory input would shut down its activity and fall asleep. However, we know by now that during sleep the brain does not shut down at all. On the contrary, it shows orchestrated and well defined patterns of activity [1]. In particular the introduction of continuous recordings of brain electrical activity (electroencephalogram, EEG) during sleep and wakefulness [2] has greatly enriched the study of sleep. Not only has it allowed to better distinguish waking from sleep but it also has led to the discovery of rapid eye-movement (REM) sleep as a specific state, different from non-REM (NREM) sleep [3].

Sleep stages

EEG recordings revealed specific activity patterns for each vigilance state (Figure 1). Thus, wakefulness is reflected in the EEG by low voltage, fast frequency activities – also called as desynchronized or activated EEG. When eyes close in preparation for sleep, EEG alpha activity (8-13 Hz) becomes prominent, particularly in occipital regions. Such alpha activity is thought to correspond to an “idling” rhythm in visual areas. When we

fall asleep we gradually disconnect from the environment. Under normal circumstances we enter sleep via NREM sleep. NREM sleep is subdivided into different stages: A transitional state, stage 1 (N1), characterized by loss of alpha activity and the appearance of a low-voltage mixed-frequency EEG pattern with prominent theta activity (3-7 Hz). Stage 1 progresses into NREM sleep stage 2 (N2), in which the EEG shows prominent sleep spindles, brief sequences of waves at around 12-15 Hz. Finally, we enter deep NREM sleep, stage 3 (N3), where the EEG dramatically changes and now shows high voltage, slow frequency waves at around 1-2 Hz, which is why this stage is also known as slow wave sleep. During NREM sleep the transition from the low-voltage, fast activity EEG observed during wakefulness to the characteristic EEG of NREM sleep is due to the occurrence of brief periods of hyperpolarization, also called *down states*, in thalamocortical and cortical neurons (for reviews see: [4]). The resulting slow oscillation is found in virtually every cortical neuron, and is synchronized across much of the cortical mantle by cortico-cortical connections, which is why the EEG records high-voltage, low frequency waves. In the course of a night NREM sleep alternates with REM sleep. During REM sleep the EEG shows low voltage, fast activity similar to wakefulness, which is why it is also referred to as paradoxical sleep [5].

Sleep quality and sleep homeostasis

It was discovered early on that arousal thresholds – measured for example as the duration of an acoustic stimulus required to awaken a sleeping subject – is positively correlated with the amount of slow-waves in the EEG of NREM sleep. It was also noticed that high amplitude slow waves predominate the first two hours

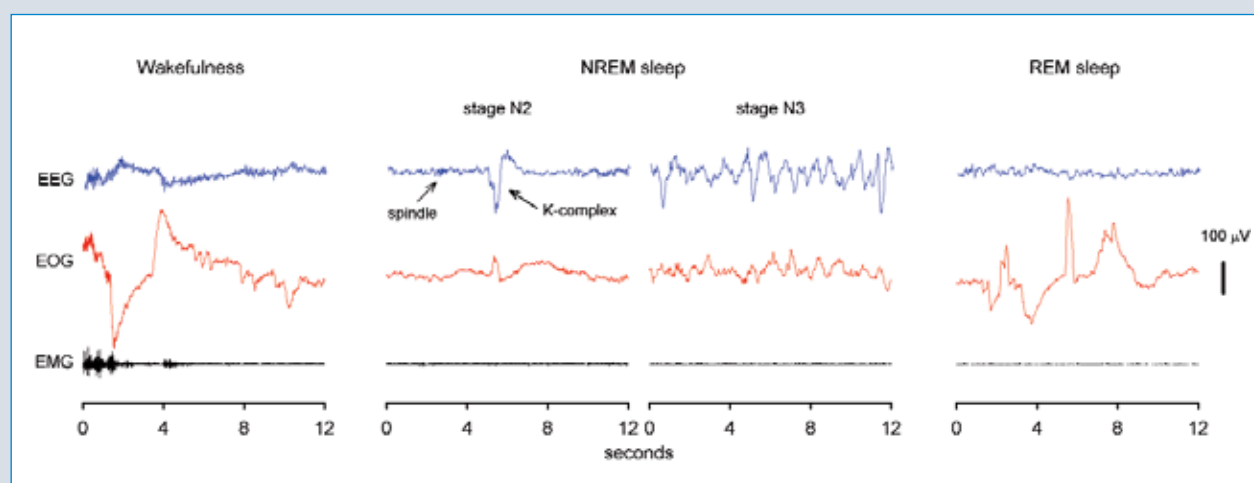


Figure 1: Vigilance states. 12-s Electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) traces are plotted for the three vigilance states wakefulness, NREM sleep and REM sleep. NREM sleep is subdivided into 3 sub-states of which stage N2 and N3 are illustrated. Stage N3 is also called slow-wave sleep. The typical EEG features of human stage 2 sleep, spindles and K-complexes are highlighted by arrows. EEG calibration marks correspond to 100 µV/0.25Hz.

of sleep and decrease thereafter [6]. It was later shown that the amount of slow wave sleep is positively correlated with the duration of prior waking [7]. The positive relationship between slow waves and the duration of wakefulness is best seen under the influence of sleep deprivation. If we are not allowed to sleep and are forced to stay awake longer than usual, sleep pressure mounts and soon becomes overwhelming. Thus, sleep is homeostatically regulated: the longer we stay awake, the longer and more intensely we sleep afterwards: arousal thresholds increase, and during NREM sleep the amplitude and prevalence of slow waves becomes much higher.

Two process model of sleep regulation

The two process model of sleep regulation provides a conceptual framework that is frequently used in the interpretation of sleep studies. This model postulates that sleep propensity is determined by the interaction of a homeostatic process S and a circadian process C [8]. Process S increases during waking and decreases during sleep. An important advance has been the demonstration that Process S is reflected accurately by the amount of slow wave activity (SWA, electroencephalographic (EEG) power in the low frequency range between 0.5 and 4.5 Hz) during NREM sleep [8, 9]. As repeatedly shown in both humans and mammals, SWA increases exponentially with the duration of prior wakefulness and decreases exponentially during sleep, thus reflecting the accumulation of sleep pressure during wake-

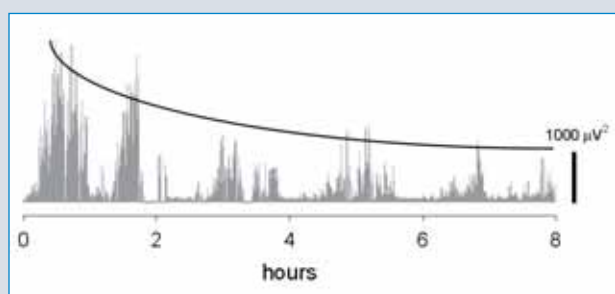


Figure 2: Slow-wave activity. Time course of EEG slow-wave activity (power density in the 0.75-4.5 Hz frequency range) during an 8-h nocturnal sleep episode of a 23-year-old, healthy man. The solid line indicates the exponential decline of SWA during the night.

fulness and its release during sleep (Figure 2). Therefore, the immediate history of sleep and waking determines the level of Process S.

In contrast, process C does not depend on the prior history of sleep but is generated by an intrinsic pacemaker located in the suprachiasmatic nuclei (SCN) of the hypothalamus. Process C is thought to modulate the timing of sleep episodes by enforcing an upper and a lower threshold so that whenever one of these thresh-

olds is reached by process S a sleep episode is terminated or initiated.

One important concept of the model is that NREM sleep loss can be recovered by an intensification of NREM sleep, reflected in a SWA increase, and not necessarily by an increase in duration. A second important concept is that the homeostatic and the circadian processes operate independently. This has been confirmed by sleep deprivation studies in SCN-lesioned rats. These animals no longer exhibit circadian modulation of sleep and wakefulness. Nevertheless sleep deprivation still results in an increase of SWA [10].

The two process model of sleep regulation has been tested under numerous experimental designs [11] and in several mammalian species including: rats, guinea pigs, and mice [12]. In these studies predictions of the time course of Process S are based on a mathematical model of its dynamics [13]. Such an approach allows a precise quantification of the dynamics of Process S and has been used to search for genes underlying the homeostatic regulation of sleep [14].

Functions of sleep

Why we sleep is one of the most mysterious remaining questions in biology. The simplest possible answer would be that sleep is just a time filler, a way to avoid trouble at times of day (or night) during which it is not safe to look for food or mates. Depending on the species, both the amount and the quality of sleep might be adjusted so as to fit the ecological niche. However, such an ecological hypothesis seems at odds with some key observations. First, sleep appears to be universal. All animal species studied so far sleep, from invertebrates such as fruit flies and bees to birds and mammals [12]. Even animals who need continuous vigilance while swimming or flying, for example certain dolphins and migrating birds, have developed alternating unihemispheric sleep rather than eliminating sleep altogether [15]. If sleep were dispensable, one would think that in such cases it would have disappeared. Second, sleep is carefully regulated. As we have seen, the longer we stay awake, the more and the more intensely do we need to sleep. This homeostatic regulation of sleep appears too to be universal, not just in mammals and birds, but even in fruit flies [12, 16]. Usually, if something is regulated, it serves some important function. Third, lack of sleep has deleterious consequences, especially for the brain. In humans, for example, the most prominent effect of total sleep deprivation, and even of sleep restriction (for several nights), is cognitive impairment, with striking practical consequences [17]. A sleep-deprived person tends to take longer to respond to stimuli, particularly when tasks are monotonous and low in cognitive demands. However, sleep deprivation produces more than just decreased alertness. Tasks emphasizing higher cognitive functions, such as logical reasoning,

encoding, decoding and parsing complex sentences; complex subtraction tasks and tasks involving a flexible thinking style and the ability to focus on a large number of goals simultaneously, are all significantly affected even after one single night of sleep deprivation [18]. Tasks requiring sustained attention, such as those including goal-directed activities, can be impaired by even a few hours of sleep loss [18]. For example, a recent study showed that medical interns make more frequent serious diagnostic errors when they worked frequent shifts of 24 hours or more than when they worked shorter shifts [19]. Only sleep and not rest can reverse these detrimental effects of sleep deprivation. As Dr. Rechtschaffen says: "You can rest all you like and you still need sleep." And finally, unless sleep served an important function, why should we engage every night in prolonged periods of immobility during which we are dangerously out of touch with the environment?

Sleep and memory

In the last decade, numerous studies appeared that seem to support a role for sleep in learning and memory. Specifically, a growing number of studies have demonstrated that sleep can enhance performance of tasks learned during prior wakefulness [20]. This enhancement is not merely time-dependent, but specifically requires sleep, and is independent of circadian factors [21]. Using a variety of behavioral paradigms, evidence of sleep-dependent memory enhancement has been found in humans and nonhuman primates such as cats, rats, mice, and zebra finches [21]. Initial studies focused on a role for REM sleep [22], but more recent studies have emphasized the importance of NREM sleep [23], of specific components within NREM sleep such as spindles [24] and slow waves [16, 25], and of a combination of NREM and REM sleep [26]. Taken together, behavioral studies in humans and other species leave little doubt that sleep plays a critical role in learning and memory.

How sleep might promote performance enhancement is not yet understood. An intriguing possibility is that the off-line reactivation during sleep of circuits involved in learning during wakefulness, and perhaps the involvement of other, connected circuits, might promote memory consolidation. Several studies in animals have shown that, during NREM sleep after learning, there is an increased correlation in the firing of cells co-activated during learning tasks in prior waking, primarily in the hippocampus [27]. In humans, neuroimaging studies have shown that hippocampal areas that are activated during route learning in a virtual town are likewise activated during subsequent NREM sleep [28]. EEG studies have shown an increase in NREM spindle density after learning pairs of unrelated words as compared to a non-learning task [24]. Similar findings have been reported after learning a maze task [29]. Finally, high-

density EEG recordings show that a visuomotor learning task, compared to a control non-learning task, produces an increase in SWA that is localized to the brain region (right parietal cortex) that is known to be involved in learning the task [30]. Many unknowns remain, however. Whether sleep may favor the consolidation of newly established memories or the maintenance of older ones is not clear. The molecular correlates of such processes are still unclear. For example, molecular markers of memory acquisition are turned off during sleep [31], which may be advantageous given that the intense neural activity of sleep occurs while the animal is disconnected from the environment. Nevertheless, evidence exists that neural activity during NREM sleep may promote brain plasticity [32], especially in developing animals [33].

Sleep and brain restitution

When we have been awake too long we say we are tired, and after sleep we feel refreshed. Not surprisingly, the most intuitively compelling idea about the function of sleep is that sleep may restore some precious fuel or energy charge that was depleted during wakefulness. It is likely that sleep may indeed reduce energy waste by enforcing body rest in animals with high metabolic rates. However, in humans the metabolic savings of spending the night asleep rather than quietly awake are no more than a slice of bread [34]. Moreover, we also say we are tired after muscle exertions, yet most bodily organs can recover through quiet wakefulness and do not need sleep. The notable exception is the brain: if we do not sleep, even though we may remain immobile, we rapidly suffer cognitive impairment. Therefore most researchers agree that sleep may be especially important for restoring the brain, and provide something not afforded by quiet waking. However, there is great uncertainty when it comes to what might actually accumulate (or deplete) during waking and be restored during sleep. A long search for humoral factors that might accumulate in the brain during wakefulness has not been successful [35]. One of the best studied substances is adenosine, not surprising given the well-known anti-sleep effect of the A1 antagonist caffeine [36]. Extracellular adenosine accumulates in the basal forebrain area during wakefulness, inhibiting cholinergic neurons and promoting sleep [37], although the importance of this feedback mechanism has recently been disputed [38]. Also, in humans, extracellular adenosine does not seem to accumulate in several brain areas as a function of previous wakefulness [39]. Prostaglandin D₂, another sleep promoting substance, acting on the prostaglandin D (PGD) receptor, indirectly activates adenosine A_{2A}-dependent pathways in the basal forebrain [40]. However, neither A₁ nor PGD receptor knockout mice have abnormal baseline sleep. Similarly, a number of lymphokines, such as interleukin-1 (IL-1) and tumor necro-

sis factor (TNF) alpha, modulate sleep. These effects are often species-specific and could be most relevant in the context of acute inflammation or infection. However, the TNF and IL-1 type I receptor knockouts have abnormal sleep, suggesting also a role in baseline sleep regulation [41].

As an alternative, it has been suggested that sleep may favor not so much the elimination of some toxic factors accumulated during wakefulness, but rather the replenishment of some important resource, for instance glycogen in glial stores [42]. However, recent evidence show that glycogen depletion may only occur in a few brain regions and only in certain strains of animals [43, 44]. The molecular changes that take place between wakefulness and sleep suggest other possibilities as well [45]: sleep could counteract synaptic fatigue by favoring the replenishment of calcium in presynaptic stores, the replenishment of glutamate vesicles, the resting of mitochondria, the synthesis of proteins, or the trafficking and recycling of membranes. Unfortunately, most of these possibilities remain unexplored.

Finally, sleep may not only be for the brain. There are indications that sleep plays a role in metabolic and endocrine regulation. For example, a recent study showed a close relationship between insulin sensitivity and the amount of slow-wave sleep [46].

Sleep and synaptic homeostasis

Memory consolidation and brain restitution are important perspectives on the function of sleep that are not mutually exclusive. Recently a comprehensive hypothesis concerning the function of NREM sleep has been advanced, the synaptic homeostasis hypothesis [47, 48]; **Figure 3**). The hypothesis, which is broadly consistent with a large body of evidence, also makes specific suggestions concerning the mechanisms leading to the increase of EEG SWA as a function of prior wakefulness. The synaptic homeostasis hypothesis proposes that plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain circuits. The main function performed by sleep is to downscale synaptic strength to a baseline level that is energetically sustainable and beneficial for memory and performance. In other words, according to the synaptic homeostasis hypothesis, sleep is the price we have to pay for plasticity, and its goal is the homeostatic regulation of the total synaptic weight impinging on neurons. An appealing feature of the synaptic homeostasis hypothesis is that it reconciles the restorative, homeostatic function of sleep with its beneficial effects on learning and memory.

The main points of the hypothesis are as follows. During wakefulness, we interact with the environment and acquire information about it. The EEG is activated, neurons are tonically depolarized and spontaneously active [1], and the neuromodulatory milieu (for exam-

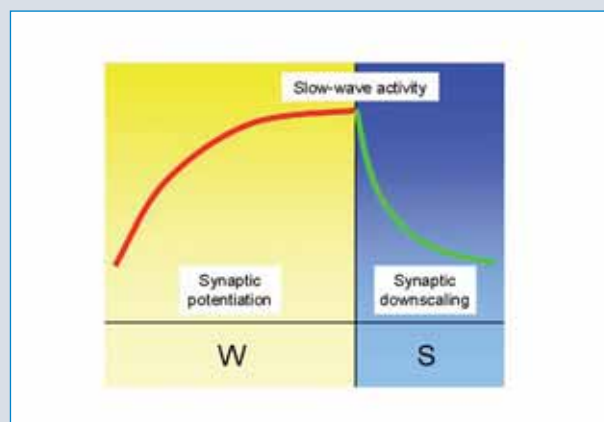


Figure 3: Synaptic homeostasis hypothesis. Synaptic strength increases during wakefulness (W) and is downscaled during sleep (S). The hypothesis proposes a close relationship between synaptic strength and sleep slow-wave activity (Figure reproduced from Tononi and Cirelli, 2006 [48]).

ple, a high level of noradrenaline, NA; [49]) favors the storage of information, which occurs largely through synaptic potentiation [50]. This potentiation occurs when the firing of a presynaptic neuron is followed by the depolarization or firing of a postsynaptic neuron, and the neuromodulatory milieu signals the occurrence of salient events [51]. A key functional corollary of the hypothesis is that, due to the net increase in synaptic strength, waking plasticity has a cost in terms of energy requirements, space requirements, supplies of key cellular constituents, and progressively saturates our capacity to learn. When we go to sleep, we become virtually disconnected from the environment [1]. Changes in neuromodulatory milieu trigger slow oscillations, comprising depolarized and hyperpolarized phases, which affect every neuron in the cortex, and that are reflected in the EEG as SWA [52]. The changed neuromodulatory milieu (e.g. low noradrenalin; [49]) also ensures that synaptic activity is not followed by synaptic potentiation, which makes adaptive sense given that synaptic activity during sleep is not driven by interactions with the environment. Since the average strength of synaptic interactions at the end of the wake period is high, neurons synchronize their firing better and the slow oscillations of early sleep are of high amplitude [53]. The slow oscillations, however, are not just an epiphenomenon of increased synaptic strength, but would have a role to play. Specifically, the repeated sequences of depolarization – hyperpolarization would lead to the downscaling of the synapses impinging on each neuron [54], meaning that they all would decrease in strength proportionally. The reduced synaptic strength reduces the amplitude and synchronization of the slow oscillations, which is reflected in a reduced SWA in the sleep EEG. Because of the dampening of the slow oscillation, downscaling is progressively reduced, making the process self-limiting when synaptic strength reaches a baseline level. By returning total synaptic weight to an appropriate baseline level, sleep enforces synaptic ho-

meostasis. Again, the key functional corollary is that synaptic homeostasis has benefits in terms of energy and space requirements, of the supply of key cellular constituents and, due to increased signal-to-noise ratios, in terms of learning and memory. Thus, when we wake up, neural circuits do preserve a trace of previous experiences, but are kept efficient at a recalibrated level of synaptic strength, and the cycle can begin again. The synaptic homeostasis hypothesis is based on a large number of observations at many different levels, from molecular and cellular biology to systems neurophysiology and neuroimaging (for more details see [47, 48]). The best electrophysiological and molecular evidence comes from a study in rats showing that wakefulness is associated with markers of cortical synaptic potentiation (e.g. increased number of synaptic AMPARs containing GluR1 subunits), whereas sleep is associated with markers of synaptic depression (e.g. dephosphorylation of synaptic GluR1; [55]). Moreover, the slopes of cortical evoked potentials, reflecting cortical excitability, increased after wakefulness and decreased after sleep. Other electrophysiological and behavioral evidence support the hypothesis [30, 56], but there are alternative explanations, and critical tests still need to be performed.

Functions of sleep and epilepsy

Seizure activity is increased during NREM sleep. More specifically, a relationship between spike and wave (SW) seizures and the EEG correlates of slow-wave sleep was repeatedly demonstrated [57]. Moreover, the frequency of interictal spiking progressively increases with the depth of NREM sleep, reaching a maximum in stage N3 [58]. By contrast, SW seizures are decreased or totally absent during REM sleep [59]. Thus, the most salient state-specific components affecting seizure activity seem to be the degree to which cellular discharge patterns are synchronized [60]. As introduced above, during NREM sleep, virtually every cell in the brain discharges synchronously [1]. On the contrary, during REM sleep and alert waking, cells discharge asynchronously [61].

Sleep deprivation is a powerful activator of seizures in nearly all types of epilepsy [62]. The effect of sleep deprivation in provoking seizures is frequently exploited in epilepsy monitoring units [63]. And even healthy subjects without a previous history of seizure have an increased seizure risk after sleep deprivation [64]. This relationship between increased sleep pressure, i.e. after sleep deprivation, and the increased seizure risk might not be by coincidence. A possible explanation is related to the function of sleep. As proposed by the synaptic homeostasis hypothesis [47, 48] synaptic strength is highest at the beginning of a night, even more so after sleep deprivation. The level of synaptic strength or weight directly relates to the level of cortical excitability. The increased excitability might be responsible for

the increased seizure probability at the beginning of a night during deep sleep or after sleep deprivation. Increased excitability results in increased synchronization of activity particularly in the slow-wave frequency range [53]. Thus, the increased synchronization might be responsible for the increased seizure risk. In the course of a night, according to the synaptic homeostasis hypothesis, downscaling occurs and as a result cortical excitability progressively decreases, decreasing the risk for seizures. Sleep deprivation, on the other hand, results in increased cortical excitability as shown in normal volunteers by means of transcranial magnetic stimulation [65]. There are even indications that the increase in cortical excitability after sleep deprivation is syndrome dependently increased in epilepsy patients [66].

What about REM sleep?

Even though much of the early research about the function of sleep was related to REM sleep, in the last decade NREM sleep got the center stage. Thus, right now, we even know less about functional aspects of the EEG during REM sleep [67]. We know that, as for NREM sleep, the amount of REM sleep is regulated. For example, when REM sleep is selectively deprived, the need for REM sleep increases and during recovery sleep is partially recovered [68]. Furthermore, several intensity parameters have been proposed for REM sleep. For example, rapid eye movement density and also EEG theta activity change as a function of prior sleep and waking [69, 70]. Most recently, theta activity during REM sleep was related to consolidation of emotional memories [71]. Using a nap paradigm the authors demonstrated a selective offline benefit of REM sleep on the consolidation of negative emotional memories. Specifically, the extent of right-dominant prefrontal theta activity during REM sleep correlated with the offline emotional memory advantage.

The controversy about the role of REM sleep in memory consolidation is best illustrated by a study where pharmacological REM sleep deprivation was used to study the effect of REM sleep suppression on memory consolidation [72]. In this study, the administration of selective serotonin or norepinephrine re-uptake inhibitors strongly reduced the amount of REM sleep, however, did not impair consolidation of skills or word-pairs in healthy men but rather enhanced gains in finger tapping accuracy.

Given the high spontaneous cortical activity, REM sleep could play a converse or similar role in synapse homeostasis as NREM sleep does [47]. Its steady depolarization and high spontaneous activity may result in strengthening of synaptic connections that are still effective after the downscaling during NREM sleep. Such a mechanism might be of particular importance during development when a high number of cortical connections are newly formed [73]. Interestingly, REM sleep

percentage is much higher in the first years of life [74]. An alternative functional consequence of the high spontaneous activity during REM sleep could be the cleansing of synapses. Uncorrelated spontaneous activity can lead to the cleansing of synapses, whereas correlated activity to a relative consolidation [73]. Thus, REM sleep could achieve, with different means, an effect partly similar to the downscaling of synapses during NREM sleep postulated by the synaptic homeostasis hypothesis [47].

Concluding remarks

Sleep is tightly regulated and its EEG shows stage specific patterns. Several of these EEG patterns seem to be related to sleep functions. Particularly, slow-waves during NREM sleep appear to be closely related to synaptic homeostasis. If indeed sleep is responsible for synaptic downscaling, as proposed by the synaptic homeostasis hypothesis [47, 48], sleep may play a central role in maintaining a balance of synaptic strength, allowing us to continuously acquire new information throughout life. Finally, the manipulation or disturbance of sleep may interact with brain diseases related to changes in cortical connectivity and excitability. One example might be the amelioration of depressive symptoms after one night of sleep deprivation in depressed subjects [75]. Nevertheless, until we fully understand the mechanism underlying the regulation of sleep such relationships between alteration in cortical functioning and sleep remain purely correlative.

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