Sleep as a synaptic architect

Raven, Frank

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CHAPTER 2

THE ROLE OF SLEEP IN REGULATING STRUCTURAL PLASTICITY AND SYNAPTIC STRENGTH: IMPLICATIONS FOR MEMORY AND COGNITIVE FUNCTION

Frank Raven, Eddy A. Van der Zee, Peter Meerlo, Robbert Havekes

Groningen Institute for Evolutionary Life Sciences (GELIFES), University of Groningen, Groningen, The Netherlands

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Summary

Dendritic spines are the major sites of synaptic transmission in the central nervous system. Alterations in the strength of synaptic connections directly affect the neuronal communication, which is crucial for brain function as well as the processing and storage of information. Sleep and sleep loss bidirectionally alter structural plasticity, by affecting spine numbers and morphology, which ultimately can affect the functional output of the brain in terms of alertness, cognition, and mood. Experimental data from studies in rodents suggest that sleep deprivation may impact structural plasticity in different ways. One of the current views, referred to as the synaptic homeostasis hypothesis, suggests that wake promotes synaptic potentiation whereas sleep facilitates synaptic downscaling. On the other hand, several studies have now shown that sleep deprivation can reduce spine density and attenuate synaptic efficacy in the hippocampus. These data are the basis for the view that sleep promotes hippocampal structural plasticity critical for memory formation. Altogether, the impact of sleep and sleep loss may vary between regions of the brain. A better understanding of the role that sleep plays in regulating structural plasticity may ultimately lead to novel therapeutic approaches for brain disorders that are accompanied by sleep disturbances and sleep loss.

Keywords: sleep, dendritic spines, synaptic plasticity, structural plasticity, sleep deprivation, hippocampus, memory, long-term potentiation, visual cortex, motor cortex

Abbreviations

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CA: Cornu Ammonis
CaMKII: Ca2+/calmodulin-dependent protein kinase II
cAMP: cyclic adenosine monophosphate
CREB: cAMP response element-binding protein
GABA: γ-Aminobutyric acid
LTP: long-term potentiation
mTOR: mammalian target of rapamycin
NLG1: neuroligin-1
NMDA: N-Methyl-D-aspartic acid
NREM: non-rapid eye movement
ODP: ocular dominance plasticity
OSRP: orientation specific response potentiation
PDE: phosphodiesterase
PKA: cAMP-dependent protein kinase; protein kinase A
REM: rapid eye movement

Introduction

It is estimated that the human brain consists of approximately 86 billion neurons and every single neuron can be connected with thousands of other neurons [1], suggesting that there are close to 100 trillion of these neuronal connections or synapses. Synapses are the locus where information is transferred from a pre- to a postsynaptic neuron [2], which is largely mediated by neurotransmitters that are released by the presynaptic axon terminals and then bind to receptors on the postsynaptic dendritic spines. The strength of these neuronal connections (i.e., synaptic strength) can be measured in several ways. In case of glutamatergic neurons, which are the focus of this review, one can measure the amount of calcium influx in the postsynaptic glutamatergic cell, postsynaptic glutamatergic receptor currents, and the expression levels of glutamate receptors. Synaptic strength can be regulated and altered, a property often referred to as synaptic plasticity or structural plasticity with the latter emphasizing changes in synaptic morphology [3, 4]. This capacity to change the strength of synaptic connections directly affects the communication between neurons, which ultimately is of crucial importance for brain function at large, in terms of reactivity to external stimuli as well as the processing and storage of information [5-7].

Dendritic spines are specialized postsynaptic membranous compartments that protrude from the dendritic shaft [8, 9] and were first identified by Santiago Ramón y Cajal at the end of the 19th century [10]. Transmission electron microscopy allowed the visualization of spines in greater detail and revealed that dendritic spines are indeed specialized compartments which contain neurotransmitter receptors, postsynaptic densities and several other organelles [11]. In recent years, a more detailed view of the spine ultrastructure was obtained with the aid of advanced imaging techniques [11-13], which has been pivotal for our developing understanding of synaptic plasticity and the way this influences synaptic function and efficacy [14]. Synaptic plasticity and regulation of synaptic strength includes the formation of new spines, spine elimination, and modifications in spine morphology [15]. It can also involve changes in neurotransmitter receptor content and thereby altering the responsiveness to neurotransmitter input [8]. Given the fundamental importance of synaptic plasticity in regulating neuronal function and communication, it is of no surprise that disruptions in synaptic plasticity and aberrant spine morphology can be observed in variety neuropsychiatric and

neurocognitive disorders [2, 16] including those that are characterized by disturbed sleep [17].

It has become increasingly clear that alterations in spine dynamics and synaptic efficacy are modulated by sleep and sleep loss, which ultimately may affect important brain functions such as alertness, information processing, cognitive function and mood [18, 19]. Indeed, even a single brief period of several hours of sleep deprivation already has a profound impact on memory [20]. Work in the last few decades has started to elucidate some of the molecular mechanisms by which sleep and sleep loss directly modulate structural plasticity in the brain and how these changes relate to memory processes including those that require the hippocampus.

Here, we review the current state of knowledge regarding the causal role of sleep in influencing spine dynamics. Subsequently, we describe recent work providing insight into the molecular mechanisms by which sleep deprivation perturbs structural and synaptic plasticity with emphasis on the hippocampus. In the final section of this review, we relate these current insights on how sleep loss affects structural plasticity and ultimately causes memory deficits, to the general hypothesis on how sleep and sleep loss impact the brain according to the synaptic homeostasis hypothesis.

Dendritic spines form the structural basis of neuronal connections in the brain

Dendritic spines consist of a base, protruding from the dendritic membrane, a neck in the middle and a head, all composed of a different mixture of actin filaments. The head is the most crucial part of the spine, containing adaptor and structural proteins, receptors and other signaling molecules important for synaptic transmission [9]. Visualization of the dendritic spine's ultrastructure, including spine shape, total length, head volume, head and neck diameter, has revealed four main categories [9, 21]. Thin spines have a long neck and relatively small head. Mushroom spines are shorter, but clearly have a larger head compared to all other spine categories. In stubby spines, on the other hand, the diameter of neck and head appear to be similar. Finally, filopodia are long, thin and lack a spine head, separating them from the other type of spines [2]. Importantly, not only is there a fair amount of variation in shape and size within each of these four categories but, also, dendritic spines are

able to rapidly change shape and shift between the different types [2, 22, 23]. Technological advances such as two-photon microscopy enabled researchers to image and follow individual dendrites and spines in vivo over a long period of time. Using this approach, it was shown that there is not only a high rate of spine turnover during young adolescence, even in adulthood and also during aging spines and their synapses can remain highly plastic [24-27]. In the adult brain, these changes in spine morphology may be driven by internal mechanisms, such as the estrous cycle [28], or occur in response to a wide variety of factors and conditions that affect brain activity, including sleep, stress, and also learning and memory processes [9].

The size and shape of spines are dependent on filaments of the structural actin protein and alterations in the morphology of spines are associated with immediate changes in the balance between assembly and disassembly of actin filaments (i.e., altered actin treadmilling). In turn, altered actin dynamics modify the electrical properties and compartmentalization within the spine and results in changes in synaptic function [4, 29, 30]. The dynamic process of actin filament elongation and disruption is controlled by a balance between the activity of negative as well as positive regulators of spine stability and motility [31-36]. One of the important regulators that will be discussed in this review is cofilin, an actin-binding protein that disassembles actin filaments (see Fig. 1). The activity of cofilin itself is regulated by mean of phosphorylation; specifically, phosphorylation of the cofilin protein reduces its activity and capacity to disassemble actin filaments [37]. Cofilin was also found to modulate trafficking of glutamate AMPA receptors during synaptic potentiation [38-40]. It is suggested that elevated cofilin activity generates the actin dynamics necessary for AMPA receptor trafficking and subsequent cofilin phosphorylation (inactivation) allows actin polymerization resulting in spine growth [40]. If cofilin is not phosphorylated, its prolonged activation can lead to spine shrinkage and eventually to loss of spines [34, 41]. Profilin has the opposite function of cofilin as it polymerizes actin and promotes spine enlargement [42]. Hence, spines can occur in different morphological states and are able to change rapidly between those states through several regulatory proteins.

Sleep deprivation impacts structural plasticity and synaptic strength

Only few studies specifically examined the impact of sleep and wakefulness on synaptic remodeling. One of these studies done in adolescent and adult mice applied in vivo two-photon imaging to examine the growth and retraction of spines on the dendrites of pyramidal neurons in the sensorimotor cortex [43]. The results show that there was a constant turnover of spines and spines were formed and lost during both wakefulness and sleep. However, in the adolescent mice there was a net loss of spines of about 2% during sleep and a net gain in spines of about 1% after both spontaneous and forced wakefulness. Strikingly, in the adult mice the balance between spine loss and gain in the sensorimotor cortex was not affected by sleep and wakefulness [43]. This observation suggests that the different behavioral states only affect spine dynamics in the sensorimotor during developmental periods.

Another study applied a Golgi-Cox staining to investigate the effect of 24 hours of sleep deprivation on spine numbers of pyramidal neurons in the prefrontal cortex in both adolescent and adult rats [44]. While sleep deprivation had no effect on spine density in the prefrontal cortex of adolescent rats, it increased spine numbers in this region of aged animals. In addition, the same study found that in sleep deprived adolescent rats spine density was decreased in the CA1 area of the hippocampus [44], a sub region that is of particular importance for information processing and memory processes [45, 46].

This negative effect of sleep deprivation on spine density of hippocampal neurons is in line with our own recent work showing that a brief period of five hours of sleep deprivation leads to a 30% reduction in the number of dendritic spines of all subtypes on neurons in the CA1 in young adult mice [47]. The attenuation of spine numbers was accompanied by a significant reduction in dendrite length, raising the possibility that the loss and weakening of neuronal connectivity as a result of sleep deprivation may undermine proper information processing in the hippocampus. Such large changes in spine numbers are not uncommon for this sub-region. Fluctuations in spine numbers of similar magnitude have previously been reported in female rats across the estrous cycle [28]. Importantly, the loss of spines in the CA1 region of the dorsal hippocampus induced by five hours of sleep deprivation was reversed

by three hours of recovery sleep [47], suggesting that recovery sleep promotes spine growth. Furthermore, five hours of sleep deprivation reduced cofilin phosphorylation in total hippocampal lysates, reflecting higher activity of cofilin in the hippocampus (see Fig. 1) [47]. The increased cofilin activity as a result of sleep deprivation was directly related to the observed spine loss as inhibition of hippocampal cofilin function in sleep-deprived mice prevented the loss of dendritic spines and reduction in dendrite length [47].

It is important to note that these changes in spine numbers were specific for area CA1 as sleep deprivation did not affect the spine density of CA3 neurons in the same animals [47]. While the underlying mechanisms that account for these region-specific changes remain to be defined, there are at least two important differences between the two subpopulations of hippocampal neurons which could potentially contribute to the region-specific changes in spine density. Firstly, the cAMP-degrading phosphodiesterase isoform 4A5 (PDE4A5), which facilitates cofilin signaling (Figure 1; [47]), is abundantly expressed in CA1 neurons, but not in CA3 neurons [48]. Because PDE4A5 facilitates cofilin signaling through suppression of PKA-LIMK activity, a lack of PDE4A5 expression in CA3 neurons may leave cofilin signaling unaffected under conditions of sleep deprivation and thus prevent changes in structural plasticity in this subregion (Figure 1). Future studies will have to examine whether the absence of PDE4A5 in area CA3 directly relates to the lack of changes in spine numbers in this region under conditions of sleep deprivation. A second aspect which could contribute to the region-specific effects of sleep deprivation on spine density in CA1 and CA3 neurons, may be the different synaptic pathways that provide direct cortical input to both subregions. For example, area CA1 receives input directly from cortical layers 3-4 whereas area CA3 receives input from layer 2 [49]. In future studies it would therefore be of interest to examine and modulate the activity of these specific cortical layers and examine whether such manipulations leads to spine density changes as observed with sleep deprivation.

Related to these subregion-specific changes observed under conditions of sleep deprivation, but also plasticity throughout the brain in general, a frequently raised concern in the field of sleep research is whether the observed phenotypes are a result of stress induced by keeping the animals awake for several hours or the actual loss of sleep. To this point, it is interesting to

note that a brief period of sleep deprivation and acute stress have different effects on structural plasticity in hippocampal subregions. While five hours of sleep deprivation does not affect spine numbers in CA3 excitatory neurons [47], several hours of acute stress leads to a reduction in spine density in this hippocampal subregion [50]. In contrast, while sleep deprivation, just like the estrous cycle, leads to a robust reduction selectively in spine numbers of CA1 neurons [28, 47], acute stress elevates the spine density in this region [51]. Only repeated or chronic exposure to stress leads to a reduction of spine density in the CA1 region of the hippocampus [52]. For extended review of the impact of stress on CA1/CA3 structural plasticity, see Leuner and Shors [53]. Altogether, the available data do not provide a uniform picture on the role of sleep in the regulation of spine dynamics and the data suggests that effects of sleep deprivation depend on the brain region, and also the age of the subjects as previously suggested by Frank and Cantera [54].

The variation in reported effects of sleep deprivation on spine dynamics of excitatory neurons is paralleled by similar variation in effects of sleep deprivation on other processes involved in regulating synaptic strength and efficacy of these neurons such as the expression and regulation of ionotropic glutamate receptors (i.e., AMPA and NMDA receptors) which we will discuss in more detail below (see Fig.1). Glutamate receptors such as NMDA and AMPA receptors consist out of multiple subunits, and phosphorylation of those subunits influences for example their incorporation into the cell membrane, which contributes to spine stabilization [55-60]. However, the effects of sleep, wake, and sleep deprivation on glutamate receptor function are unclear. One study showed that in the cortex and hippocampus of adult rats the expression and phosphorylation of GluR1-subunit containing AMPA receptor was higher after spontaneous wakefulness and sleep deprivation than after sleep [61]. This finding suggests a synaptic potentiation during wakefulness and depression during sleep. However, in contrast with this finding is a study in mice reporting that 12 hours of sleep deprivation attenuated AMPA receptor phosphorylation specifically at the GluA1 subunit in the hippocampus, which was taken to suggest a reduced incorporation of these receptors in the membrane [62]. Furthermore, a brief period of four hours of sleep deprivation decreased hippocampal NMDA receptor function that was accompanied by a change in the molecular composition of synaptic NMDA receptors [63]. In the same line, neuroligin-1 (NLG1) is a postsynaptic adhesion molecule pres-

ent at glutamatergic and GABAergic synapses and is suggested to regulate the activity and localization of NMDA receptors [64, 65]. Reduced NGL1 expression in the forebrain is seen after one to six hours of sleep deprivation suggesting that sleep deprivation also negatively impacts the synaptic plasticity in the brain at the level of NLG1 [64, 65]. Altogether, while glutamatergic signaling plays an important role in synaptic plasticity that seems to be influenced by sleep deprivation, there is no clear picture on the magnitude and direction of this effect [66]. Defining the impact of sleep and sleep loss on glutamatergic signaling in the brain as a whole remains challenging as seems to exert its effects in a brain region-specific fashion [54].

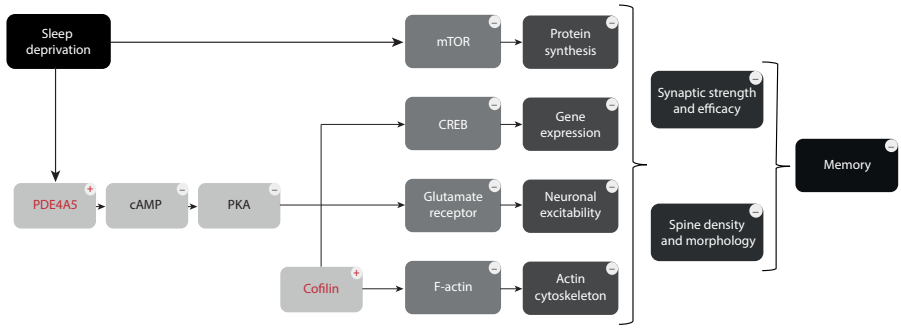
Sleep deprivation impairs synaptic plasticity critical for memory formation

One of the implications of altered regulation of structural plasticity and synaptic strength as a consequence of sleep deprivation may be an impairment of cognitive processes, particularly those that require the hippocampus [3, 59, 67]. At the end of the 19th century, Cajal already hypothesized that an increase in the strength of synaptic connections between neurons might be an underlying mechanism of memory storage [10]. However, it was half a century later when Hebb integrated the existing knowledge of memory research and proposed that the growth of new synaptic connections between specific neurons and metabolic changes within those neurons might underlie the storage of information into the brain [68]. Bliss and Lømo [69] further developed the idea of a neural basis for memory and constructed a cellular and experimental model for hippocampal learning and memory, which is now widely known as long-term potentiation (LTP). Several changes in spine morphology have been observed after LTP induction including the enlargement of the spine head, as well as the widening and shortening of the spine neck [4, 70-74]. Remarkably, such changes can occur already within minutes after LTP induction and can last at least up to a day [30, 31, 75-78]. Transient forms of LTP mainly involve proteins such as the calcium/calmodulin-dependent protein kinase ii (CaMKII) that facilitate the insertion of new AMPA glutamate receptors in the cell membrane [56, 79, 80]. In contrast, long-lasting forms of LTP depend on gene expression and protein synthesis that ultimately result in structural changes of the synapse [81, 82]. After a period of high plasticity, spine motility is reduced and spines are stabilized [83]. During the initial period of elevated plasticity, cofilin activity is increased through a reduction

in its phosphorylation. Thereafter, 15-30 minutes after LTP induction, cofilin activity returns to baseline levels, causing a normalization of actin dynamics [83, 84]. Hence, the ability of LTP to induce spine growth and eventually produce structurally and functionally mature dendritic spines may reflect a mechanism underlying maintenance of information (i.e., memory consolidation). The finding that sleep deprivation can reduce spine density in the CA1 region of the hippocampus suggests that a lack of sleep may interfere with LTP and memory consolidation. Indeed, five hours of sleep deprivation impairs some long-lasting forms of hippocampal LTP that depend on transcription and translation [85]. Moreover, these observations indicate that sleep deprivation targets specific molecular mechanisms that are involved in this form of LTP, such as the cAMP-PKA pathway. In line with this notion, basal levels cAMP levels in the hippocampus increase during rapid eye-movement (REM) sleep, and are attenuated after five hours of sleep deprivation [85, 86]. Furthermore, there is now ample evidence that the reduction in cAMP as a consequence of sleep deprivation plays a key role in the deficits of memory and behavioral performance, particularly in tasks that require the hippocampus [18, 20, 66]. More recently, a pharmacogenetic approach combined with a viral strategy was used to boost cAMP levels in all subregions of the hippocampus in order to overcome the reduction caused by sleep deprivation [87]. Transiently increasing cAMP levels, specifically in excitatory neurons of all major hippocampal subregions of sleep-deprived mice, was sufficient to prevent memory impairments in an object-location memory task. Together with previous work these findings indicate that deficits in memory and LTP associated with sleep deprivation are causally related to misregulation of cAMP signaling in the hippocampus [47, 85].

The sleep deprivation-induced reduction in hippocampal cAMP levels is now known to be a result of increased activity of the PDE4 family and elevated protein expression of the PDE4A5 isoform [85, 88]. To assess a direct role for PDE4A5 in the impaired hippocampal structural plasticity and memory deficits associated with sleep deprivation, another set of experiments tested whether suppression of PDE4A5 activity in mouse hippocampal excitatory neurons was sufficient to prevent these effects of sleep deprivation. Indeed, blocking PDE4A5 function in hippocampal neurons made memory consolidation resilient to sleep deprivation [47]. In addition, it normalized hippocampal cofilin activity in the hippocampus of sleep deprived mice suggesting a po-

tential direct role for cAMP signaling in the structural plasticity deficits associated with sleep deprivation. As mentioned above, cofilin was identified as a causal mediator of the hippocampal spine loss in sleep-deprived mice [47] raising the question whether this increase in cofilin activity was also directly related to the memory deficits observed under conditions of sleep deprivation. Indeed, suppression of cofilin function in this population of neurons not only prevented spine loss, it also made long-lasting LTP and object-location memories resilient to the debilitating effect of sleep deprivation [47]. All in all, these studies indicate that sleep loss leads to spine loss in adult mice, and hampers long-lasting forms of hippocampal synaptic plasticity and memory, with a pivotal role for PDE4A5 and cofilin (see Fig.1).



▲**Figure 1**: *Overview of molecular mechanisms through which sleep deprivation hampers hippocampal memory consolidation. Signaling molecules and pathways whose function is reduced after sleep deprivation are indicated by a minus (-). Signaling molecules and pathways whose function is promoted by sleep deprivation are indicated by a plus sign (+). It should be noted that PKA attenuates cofilin signaling indirectly through the phosphorylation of LIMK (not shown). Abbreviations: cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein; F-actin, filamentous actin; mTOR, mammalian target of rapamycin; PDE4A5, phosphodiesterase 4A5; PKA, cAMP-dependent protein kinase.*

Another consequence of sleep deprivation-induced attenuation of hippocampal cAMP-PKA signaling is a change in the regulation of gene expression by the transcription factor cAMP-response element binding protein (CREB). Indeed, while phosphorylation and activation of CREB is increased during REM sleep [86], phospho-CREB was found to be reduced [85, 89]. Also, five hours of sleep deprivation leads to decreased expression and activity of mammalian target of rapamycin (mTOR) a serine/threonine kinase that together with regulatory-associated protein of mTOR (Raptor) releases the break on protein synthesis initiation [90]. Attenuated CREB-mediated gene regulation and mTOR-orchestrated protein synthesis as a consequence of sleep loss may

ultimately limit structural plasticity and memory processes (see Fig.1) [91, 92]. This critical role for mTOR signaling and de novo protein synthesis in sleep-dependent forms of synaptic plasticity is not limited to the hippocampus as sleep-dependent consolidation of plasticity in the visual cortex also requires mTOR-mediated translation. Blocking mTOR with rapamycin during sleep disrupted the consolidation of this form of synaptic plasticity [93]. Altogether the work described in this section suggests that similar molecular mechanisms contribute to sleep-dependent forms of synaptic plasticity in the hippocampus and visual cortex.

Sleep, sleep deprivation and synaptic homeostasis

While ample evidence exists for the role of sleep in promoting structural plasticity and synaptic strength in memory processes, other views on the role of sleep in structural plasticity have emerged. One of most prominent hypothesis in this respect is the synaptic homeostasis hypothesis, as postulated by Tononi and Cirelli [94-96]. This hypothesis holds that, overall, wakefulness is linked to a net increase in synaptic strength in many brain circuits. Such a gradual and ongoing potentiation might not be energetically sustainable and could eventually hamper further processing of new information. Sleep therefore would serve to reverse this potentiation by a global synaptic downscaling throughout the brain. Downscaling would globally decrease synaptic strength to a similar level as before wakefulness, which has benefits in terms of energy requirements and allows for processing of new input. Initially, the downscaling process was thought to be non-specific affecting all synapses, but the current view is that the downscaling may particularly affect the weaker synapses while leaving strong synapses intact. The downscaling would thus contribute to an improved signal-to-noise ratio by reducing the noise (global downscaling) while preserving specific signal (competitive down-selection) [96].

The synaptic homeostasis theory has driven enormous amounts of empirical studies some of which provided data in apparent support of this hypothesis. For example, as discussed in an earlier section the ratio of spine formation versus elimination varies with sleep deprivation. Specifically, in young mice it was found that there was a net gain in the number of spines in the somatosensory cortex during wakefulness and a loss of spines in this region during sleep [43]. In addition to these changes in structural plasticity studies in rats

have reported changes in glutamate receptor expression and function also in line with synaptic homeostasis [61]. Cortical and hippocampal GluA1 subunit-containing AMPA receptor expression and phosphorylation were elevated after a period of spontaneous wake or sleep deprivation as compared to sleep [61].

In a recent paper De Vivo et al. [97] studied the effects of sleep and wakefulness on spine head volume and axon-spine interface using 3D electron microscopy in the mouse motor and sensory cortex. Both spine head volume and axon-spine interface were smaller after a period of sleep as compared to a period of either spontaneous wakefulness or enforced wakefulness. The axon-spine interface in the cortex of mice after a period of sleep was about 18% smaller than it was in mice after a period of wakefulness. The reduction was proportional to axon-spine interface size. Furthermore, the downscaling was observed specifically in the smaller and weaker synapses whereas the larger and stronger synapses remained stable. These findings are in accordance with the hypothesis that sleep serves for downscaling of synapses, at least in the M1 motor cortex and S1 sensory cortex.

In addition, a recent study suggests that weakening of synapses in the cortex during sleep may in part be associated with the removal and dephosphorylation of synaptic AMPA receptors [98]. Furthermore, they suggest that this was driven by the immediate early gene Homer1a and signaling from group I metabotropic glutamate receptors mGluR1/5. Specifically, Homer1a levels increased in neurons during wake, however, Homer1a moves towards the PSD during sleep causing synapse weakening, probably as a result of a decline in noradrenaline. These studies by De Vivo et al [97] and Diering et al [98] indicate that sleep and sleep deprivation by means of exposing animals to novel objects [97] or a clean standard mouse cage combined with gentle handling [98] respectively may lead to global synaptic downscaling in these cortical regions. However, it does not exclude the possibility that specific sleep stages and sleep deprivation affect neuronal plasticity and structure in a layer-specific fashion and depresses stronger synapses less than weaker ones as described in the next paragraphs.

Clearly, not all available data are in full agreement with a role for sleep in global downscaling. Recent studies by the lab of Gan examined the differen-

tial effects of REM and non-rapid eye movement (NREM) sleep on spine dynamics in the mouse motor cortex during development and after motor learning [99]. They observed that REM sleep has a bidirectional role in regulating spine dynamics. Specifically, REM sleep selectively pruned some newly formed spines during development and after motor learning, indicating a role for REM sleep in unlearning by removing excessive synaptic connections. REM sleep also promoted the maintenance of other newly formed spines during both development and motor learning, thereby facilitating their incorporation into existing synaptic circuits. Using pharmacological approaches the authors showed that NMDAR activation and downstream calcium signaling are required for the selective pruning and strengthening of new spines. These findings complement their previous work showing that NREM sleep after motor learning is important for branch-specific spine formation and survival in layer 5 of the motor cortex [100]. Thus, the effect of REM sleep overall appears to be bidirectional, able to increase the strength of a fraction of new spines that persist over time while also eliminating most of the newly formed spines and thereby regulating the number of learning-induced new synapses over time. These results are in accordance with an earlier study [101], which used medial lemniscus stimulation to record evoked potential responses in the somatosensory cortex during wake/sleep transitions from non-anesthetized cats to investigate the effect of slow-wave sleep (SWS, the deepest stage of NREM sleep) on synaptic plasticity. They found that the evoked potentials during wake were increased after a SWS episode as compared with a previous wake episode. This indicates that it is indeed possible that sleep, and specifically SWS, offers an opportunity for long-term potentiation to contribute to memory consolidation. However, not all studies measuring evoked responses show a clear relation between synaptic strength, LTP or LTP-like plasticity under conditions of sleep deprivation. For example, recent work by Kuhn et al [102] demonstrated that indices of increased net synaptic strength and decreased LTP-like plasticity in the human cortex after one night of sleep deprivation.

Also, other studies have provided data that do not appear to be in line with the synaptic homeostasis hypothesis. As discussed in the previous sections, the effect of sleep deprivation on spine formation and synaptic strength and efficacy may depend on various factors such as brain region and age of the subjects [54], but overall the picture is not fully clear. In adult mice, extend-

ed wakefulness resulted in a loss of synaptic spines in the CA1 region of the hippocampus [47], and a reduction of AMPA receptor phosphorylation [62]. Moreover, as little as three hours of recovery sleep is sufficient to restore spine density [47], suggesting that sleep may promote spine formation, in contrast to the prediction of the synaptic homeostasis theory.

In another study, visual responses and spontaneous activity were recorded from V1 neurons of the visual cortex before and after presentation of a visual stimulus to induce enhanced V1 responses to stimuli of the same orientation (orientation specific response potentiation, OSRP) [103]. Then, changes in OSRP were measured after subsequent sleep or sleep deprivation. Results indicated that OSRP expression is indeed associated with cortical synaptic potentiation (i.e. the mean neuronal firing rates in V1 were increased over a period of several hours [103], and selective to the presented stimulus [104] and required sleep as a short period of sleep deprivation impaired OSRP formation. Hence, these findings show that synapses are potentiated rather than downscaled during sleep. In line with these observations, work by the Frank lab examined the impact of sleep deprivation on ocular dominance plasticity (ODP), a form of cortical plasticity that is induced by transiently blocking patterned vision in one eye (also referred to as monocular deprivation) [105]. They found that this form of cortical plasticity is also supported by sleep, and depends on NMDA receptor and PKA activation [106]. Thus, sleep deprivation impacts similar molecular signaling pathways critical for synaptic plasticity in hippocampal and visual cortical circuits. While it recently has been suggested that the use of sensory evoked responses in isolation may not be an adequate proxy for synaptic strength [107], it is important to note that work of the lab of Mark Bear has shown that OSRP can be considered as an in vivo form of long-term potentiation of glutamatergic synapses in the visual cortex as it depends on the same cellular mechanisms [108]. Furthermore, OSRP leads to a reduction in the magnitude of in vivo-evoked thalamocortical LTP and vice versa [109].

Altogether, while there is a substantial amount of literature arguing for synaptic downscaling across sleep, recent work from different laboratories support the opposing view that sleep promotes synapse formation and sleep deprivation leads to synaptic loss. The direction of synaptic changes during sleep, therefore, remains a heavily discussed topic [110-112]. While sleep depriva-

tion may have region-specific effects on synaptic and structural plasticity that could account for some of these discrepancies [54], one other aspect may explain the opposing findings is the method by which rodents are being kept awake. Whereas studies using the gentle handling method (also referred to as mild stimulation method) find that sleep deprivation attenuates hippocampal synaptic plasticity and leads to spine shrinkage (for example, [47, 62, 66, 85, 93, 106]), using novel objects or context to keep animals awake seems to lead to synaptic potentiation in accordance with the hypothesis that sleep serves for downscaling of synapses [61, 97]. While this difference in the method used to keep animals awake may seem like a minor detail, it should be noted that exploration of new environments and novel objects facilitates NMDA and AMPA receptor subunit phosphorylation and activates ERK 1/2 in both the hippocampus and prefrontal cortex [113]. Furthermore, exposure to object novelty causes depotentiation of previously induced LTP in vivo [114]. For this reason we believe it is essential to conduct side-by-side studies assessing the impact of the two different methods of sleep deprivation on synaptic and structural plasticity in the hippocampal and cortical regions.

Conclusions

As humans spend one third of their life asleep, sleep must have an evolutionary advantage and be of fundamental importance for proper brain function. Chronically restricted and disrupted sleep is a serious problem as a result of our modern life style, high workload, shiftwork, psychosocial stress, and sleep disorders such as insomnia. Indeed, chronically disrupted sleep has been identified as a risk factor in a wide variety of disorders such as psychiatric disorders and can have serious repercussions and even fatal consequences in a matter of months or years [115]. Because sleep is considered to play an essential role in regulating brain plasticity, understanding the role of sleep at the molecular level is therefore of the utmost importance to gain insight into normal brain function and fundamental processes such as memory formation. In addition, it is also pivotal to gain insight into the pathological consequences of chronically disrupted sleep as it so often occurs in our society. Nevertheless the molecular and neurobiological underpinnings are often unclear.

It is widely acknowledged that structural plasticity and synaptic efficacy play a critical role in proper information processing. Indeed, alterations in spine

numbers and morphology and resulting changes in synaptic efficacy are generally accepted to be essential for memory formation including those that depend on the hippocampus. As a result the mechanism by which sleep modulates structural plasticity critical for cognitive processes and memory has generated considerable interest. Studies examining the impact of brief or longer periods of sleep loss on brain plasticity have emphasized that the hippocampus is particularly susceptible to sleep deprivation. Therefore, it is of no surprise that hampered hippocampal function is also observed with sleep disorders such as sleep apnea, insomnia, and narcolepsy. In fact, even in neuropsychiatric disorders often associated with sleep loss, impaired functioning of the hippocampus is commonly reported.

Recent work has started to elucidate some of the mechanisms by which loss of sleep perturbs proper information processing in the hippocampus through misregulation of structural plasticity and synaptic efficacy. The changes in spine dynamics in the hippocampus following a brief period of sleep deprivation are at least in part the result of hampered cAMP signaling and translation processes (see Fig.1). These alterations in hippocampal neuronal connectivity may also explain the reduction of hippocampal volume in rodents subjected to more chronic partial sleep deprivation [116], and patients that suffer from the aforementioned sleep disorders such as sleep apnea [117], and primary insomnia [118]. Defining whether the molecular pathways affected by a brief period of sleep deprivation contribute to the hippocampal shrinkage and malfunction may ultimately provide novel therapeutic approaches to treat brain disorders that are accompanied by sleep disturbances and sleep loss.

Practice points

- The brain contains 100 trillion dendritic spines and together with their synapses form the structural basis of neuronal connections in the brain. Changes in spine morphology occur in response to a wide variety of factors and conditions such as sleep and sleep deprivation.
- Although there is evidence for synaptic downscaling across sleep as postulated by the synaptic homeostasis hypothesis, recent work focused on the hippocampus indicated that sleep promotes spine formation whereas sleep deprivation leads to the loss of dendritic spines

and attenuates synaptic efficacy in this region of the brain. The effect of sleep deprivation on structural plasticity may vary between brain regions and can depend on the age of the studied subject.

- Several molecular mechanisms modulate structural and synaptic plasticity such the as the pathways that require cAMP, glutamatergic signaling, protein synthesis through mTOR, and gene transcription. Sleep deprivation negatively impacts these signaling events.
- Hippocampal long-term potentiation (LTP) is a cellular model for memory storage. Both LTP and memory processes that require the hippocampus are particularly susceptible to sleep loss.

Research agenda

- Data on the question whether sleep deprivation facilitates or inhibits spine formation and synaptic efficacy are not consistent. This could be a result of the nature of the sleep deficiency (i.e., duration of sleep deprivation, sleep deprivation versus sleep fragmentation, different sleep stages). More research is needed to identify the critical factors that determine the direction and magnitude of changes in structural plasticity following experimental sleep deprivation.
- It is becoming more apparent that sleep and sleep loss may affect structural plasticity in an opposite fashion depending on nature of the subject (i.e., the age and sex of the subject). The data presented here leave open that the effects of sleep deprivation on structural plasticity depend on the characteristic of the subject.
- The data discussed show that impaired cAMP signaling plays a critical role in the sleep deprivation-induced memory deficits that require the hippocampus. Research is needed to define whether similar molecular mechanisms are also involved in effects of sleep loss on other aspects of brain function that depend on other brain regions.
- Very little is known about the molecular consequences of chronically disrupted sleep and how that may contribute to brain disorders including those that negatively impact structural plasticity. For example, it is unclear whether a misregulation of neuronal connectivity is also seen in brain disorders that characterized by disrupted sleep such as insomnia, sleep apnea, and narcolepsy. More experimental studies with the appropriate animal models are required to examine this possibility.
- It is essential to conduct side-by-side studies assessing the effects of different methods of sleep deprivation on synaptic and structural plasticity in the hippocampal and cortical regions.

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