

Sleep and plasticity

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Received: 17 May 2011 / Revised: 6 September 2011 / Accepted: 14 September 2011 / Published online: 27 September 2011
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Abstract While there is ample agreement that the cognitive role of sleep is explained by sleep-dependent synaptic changes, consensus is yet to be established as to the nature of these changes. Some researchers believe that sleep promotes global synaptic downscaling, leading to a non-Hebbian reset of synaptic weights that is putatively necessary for the acquisition of new memories during ensuing waking. Other investigators propose that sleep also triggers experience-dependent, Hebbian synaptic upscaling able to consolidate recently acquired memories. Here, I review the molecular and physiological evidence supporting these views, with an emphasis on the calcium signaling pathway. I argue that the available data are consistent with sleep promoting experience-dependent synaptic embossing, understood as the simultaneous non-Hebbian downscaling and Hebbian upscaling of separate but complementary sets of synapses, heterogeneously activated at the time of memory encoding and therefore differentially affected by sleep.

Keywords Adenylyl cyclase · Ca^{2+} dependence · cAMP · Electrophysiology · Gene expression · Hippocampus · Long-term potentiation · Long-term depression · Memory · Plasticity

Introduction

The involvement of sleep with learning and memory has been extensively demonstrated in various animal models

including humans [23, 25, 29, 30, 35, 50, 51, 57, 58, 60, 62, 70, 75–77, 83, 87, 89, 105, 118, 119, 136–140, 143, 144, 147, 150, 151]. Furthermore, several electrophysiological and imaging studies provide comprehensive support and mechanistic basis for the notion that sleep promotes cognitive processing [22, 37, 53, 54, 59, 61, 67, 71, 80, 82, 83, 88, 90, 98, 99, 104, 109, 117, 148]. Recently, it was shown that memory quickly undergoes consolidation when reactivated during sleep while becoming labile after being reactivated during waking [25]. In relationship with these findings, most if not all sleep researchers agree that sleep promotes brain plasticity, understood as lasting changes in the strength of synaptic connections. But here the consensus ends, for at least two different views currently coexist in the literature.

One group of researchers postulate that sleep is fundamentally a state of synaptic downscaling, a homeostatic process by which synaptic weights saturated during waking would decrease to baseline levels, so as to enable further potentiation during subsequent waking [126, 127]. The proponents of this theory believe that sleep is associated with a net decrease of synaptic strength, while wakefulness produces the opposite effect, i.e., a net increase of synaptic strength. This view is mainly supported by evidence of (1) sleep-dependent downregulation of activity-dependent gene transcripts, metabolic enzymes, calcium-dependent protein kinases, and membrane trafficking proteins [135]; (2) electrophysiological potentiation during waking, with depotentiation during sleep [64, 135]; and (3) morphological enhancement of synapses during waking, with a reduction during sleep [7].

At partial odds with the notion presented above, an alternative view proposes that neuronal circuits may also undergo experience-dependent upscaling of synaptic weights during sleep, depending on the conditions of memory acquisition [23, 102]. This notion is originally

This article is published as part of the Special Issue on Sleep.

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grounded on experiments showing that post-learning sleep elicits an upregulation of the levels of calcium-dependent transcripts and proteins related to synaptic upscaling [100, 101, 104, 106, 133]. This body of data agrees well with the demonstration that sleep deprivation impairs calcium signaling required for synaptic upscaling in the hippocampus [134]. Further support for this view comes from the investigation of the role of sleep during development [2, 33, 66, 112–115]. Very compelling evidence for synaptic upscaling during sleep has also been uncovered in fruit flies [26, 39].

The first aim of this article is to review the bodies of evidence regarding synaptic downscaling and upscaling during sleep. Despite the fact that the two conflicting theories are based on different assumptions and experimental strategies, the second aim of this article is to argue that the data available are actually compatible and complementary, in the sense that separate neuronal circuits undergo differential plasticity during sleep, leading to synaptic embossing [93, 103].

Evidence of synaptic downscaling during sleep

Donald Hebb was the first to clearly postulate that memory formation at the level of neuronal circuits requires the joint firing of pre- and post-synaptic neurons, which would lead to a local enhancement of synaptic efficacy and to a short-term period of electrophysiological reverberation [49]. In addition, he proposed that long-term mnemonic consolidation should be critically dependent on the occurrence of morphological changes capable of producing lasting modifications on the strength of synaptic connections [49], a well-established fact nowadays [21, 44, 45, 141, 145]. The amnesic effect of protein synthesis blockers demonstrated decades ago that such morphological changes require de novo protein synthesis [42]. Since then, we learned that this process is governed by the activation of specific signaling cascades and gene expression programs [4, 74]. Long-term Hebbian plasticity is elicited by synchronous pre-synaptic firing that leads to sustained post-synaptic depolarization, capable of opening *N*-methyl *D*-aspartate (NMDA) channels [69], which allow for increased calcium entry and the consequent phosphorylation of calcium-dependent protein kinases [5, 34, 63]. The process eventually leads to the transcriptional upregulation of immediate early genes (IEG), which encode a variety of proteins related to changes in gene regulation and synaptic morphophysiology. Some IEG are direct effectors of neuronal plasticity, while other IEG code for indirect modulators of cell functioning, such as transcriptional regulators.

An important plasticity-related effector gene encodes for the activity-regulated cytoskeleton-associated (*arc*) protein,

a calcium-dependent IEG that promotes synaptic remodeling by way of interactions with actin, glutamatergic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and calcium/calmodulin-dependent protein kinase II (CaMKII). *Arc* mRNA is transported for local translation in dendrites, likely playing an important role in tagging specific synapses for plasticity [47, 68, 120, 142]. The gene *zif*-268 (homologous to *egr*-1, *NGFI*-A, *krox*-24, and *ZENK*) is an example of a calcium-dependent gene with a regulatory plasticity function. *Zif*-268 encodes a transcription factor that putatively modulates the expression of hundreds of different genes [8, 78, 149], including synapsins I and II [92, 125], which are crucially involved in synaptic vesicle release [52].

The first attempt to assess the existence of sleep-dependent synaptic plasticity involved the use of protein synthesis blockers. This early experiment established a role for de novo protein synthesis in the cognitive effects of sleep because the blockade of protein synthesis during post-learning sleep markedly impairs memory consolidation [46]. With the discovery of calcium-dependent IEG in the late 1980s, many of which encode transcription factors required for memory consolidation, sleep researchers envisioned a causal Hebbian mechanism able to link short-term electrophysiological activation to long-lasting changes in synaptic morphophysiology. The reasoning at this point was quite straightforward: If sleep promotes memory consolidation and IEG are necessary for long-term plasticity, *ergo* the expression of IEG should be upregulated during sleep.

Contrary to this prediction, however, the pioneer assessments of the question found that rats investigated after long periods of sleep showed low levels of mRNA and protein encoded by the IEG *c-fos* and *NGFI*-A (*zif*-268), in comparison with the increased levels detected in sleep-deprived animals [94–97, 129]. Soon later, these results were confirmed by another group [85]. Eventually, the observations were extended to other IEG [9, 12, 13, 15–19, 48, 128], calcium-dependent kinases, and other molecular markers of plasticity [135]. Additional support for synaptic downscaling during sleep comes from electrophysiological experiments in rats showing that the slope and amplitude of cortical evoked responses increase after waking but decrease after sleep [135]. Likewise, miniature excitatory post-synaptic currents recorded from rodent cortical slices are larger and more frequent after periods of waking than after periods of sleep [64]. A computational model that fits the data has been published [86].

Synaptic downscaling during sleep was proposed to be a general feature of vertebrates, as well as invertebrates, because studies in *Drosophila melanogaster* found that periods of sleep were associated with an increase in the levels of transcripts related to membrane trafficking proteins and a decrease in the expression levels of metabolic enzymes such as cytochromes, which are

essential for respiration within mitochondria [6, 10, 11, 14, 56, 116]. Furthermore, sleep was also associated with the transcriptional downregulation of the IEG arc, homer, and zif-268, as well as the brain-derived neurotrophic factor (BDNF) [13]. Very recently, a combination of *Drosophila* genetics with confocal microscopy and behavioral analysis directly showed that the size and number of synapses increase after waking and decrease after sleep [7]. Synaptic growth was even more prominent when a richer waking experience was provided. The study also investigated the role of the gene fragile X mental retardation 1 (Fmr1) in sleep-dependent synaptic renormalization. Fmr1 overexpression in the fruit fly brain abolished the wake-dependent increase in spine number, adding support to the notion that this gene plays a role in synaptic pruning [7].

Taken together, these results have been used to support the “synaptic homeostasis hypothesis” (SHY) proposed by Giulio Tononi and Chiara Cirelli [126, 127], by which sleep promotes a non-Hebbian downward adjustment of synaptic weights at the network level, in contrast to classic Hebbian forms of plasticity that act on specific circuits. SHY is intimately related to a more general principle called homeostatic synaptic plasticity, proposed by Gina Turrigiano to describe generalized synaptic scaling capable of maintaining the functional stability of neuronal circuits subjected to cumulative activity-dependent changes [130, 131]. According to this principle, a non-Hebbian negative feedback on the number and efficacy of synapses would counterbalance the positive feedback that characterizes Hebbian plasticity, leading to a renormalization of synaptic weights that would enable further Hebbian changes [132].

Evidence of synaptic upscaling during sleep

At variance with the findings described above, other research teams including mine have generated quite different results, based on distinct assumptions and therefore distinct experimental designs. To assess the mnemonic role of sleep, these experiments always took into account the need to compare animal groups with and without exposure to novel stimulation [41]. Furthermore, the experiments were designed to sort and compare the distinct contributions of slow-wave sleep (SWS) and rapid eye movement sleep (REM) because these states are characterized by quite different durations and neuronal activity regimes. Since SWS is much more abundant than REM [40], experiments that do not attempt to separate sleep states are dominated by SWS and therefore fail to address the effects of REM [13].

By adopting an experimental design with pre-sleep exposure to a novel environment and SWS/REM state sorting, I verified in rats that the first REM episode after

exploration of a novel environment elicits an upregulation of zif-268 mRNA levels in the cerebral cortex and hippocampus, a phenomenon not observed in non-stimulated controls [100]. On the other hand, SWS consistently correlated with decreased zif-268 mRNA levels irrespective of prior exposure to novelty [100]. These results were corroborated by a subsequent study in which novel environment exploration was substituted by high-frequency stimulation of the hippocampus [101], a protocol used to induce long-term potentiation (LTP) [4]. The experiments revealed three spatiotemporally distinct waves of zif-268 expression, beginning proximally in the hippocampus 30 min after stimulation and reaching distal cortical and subcortical regions during the two ensuing REM episodes a few hours after LTP induction. Every wave of zif-268 mRNA upregulation initiated during REM, continued through waking, and was stopped by the subsequent SWS episode. Taken together, the data pointed to the existence of intermittent hippocampofugal plasticity as the sleep–wake cycle recurs, with synaptic downscaling favored by SWS and synaptic upscaling elicited by REM [101].

A few years later, the evidence of experience-dependent synaptic upscaling during REM was extended to other plasticity-related factors. An independent research group verified that, in rats trained in the active avoidance learning task, REM induces an experience-dependent upregulation of arc and BDNF protein levels, as well as an increased phosphorylation of the cyclic adenosine monophosphate response element-binding (CREB) protein [133]. In agreement with these data, my group went on to show that zif-268 and arc mRNA levels continue to be upregulated by REM in the cerebral cortex (but not in the hippocampus) after dozens of post-novelty sleep cycles have elapsed [104]. One important finding of this study is that IEG upregulation elicited by post-novelty REM was strongly and positively correlated with the amplitude of local field potentials in the frequency range of spindles (10–14 Hz), neural oscillations associated with learning and LTP [20, 27, 31, 32, 36, 79, 81, 83, 107, 108, 122–124, 146]. In contrast, IEG mRNA levels after post-novelty REM were not well correlated with firing rates. These results are in line with the notion that IEG expression is more related to dendritic inputs than to somatic outputs (action potentials) [65, 84]. The data indicate that cortical spindles, which are particularly abundant in the transition between SWS and REM [40], may couple the robust mnemonic reverberation that characterizes the former [22, 37, 53, 54, 59, 61, 67, 71, 80, 82, 83, 88, 90, 98, 99, 104, 109, 117, 148] to the IEG transcriptional upregulation triggered by the latter [39, 100, 101, 104, 133]. Such a mechanism could in principle explain the cognitive complementarity of the two main sleep states [41, 77, 121].

The investigation of sleep in invertebrates also yielded evidence of synaptic upscaling. Socially enriched fruit flies exposed to many males and females displayed significantly more sleep than socially impoverished isogenic siblings that were individually housed [39]. Sleep was modified by the most recent social experience so that socially impoverished flies with short sleep became longer sleepers when exposed to social enrichment; conversely, socially enriched flies with long sleep became short sleepers when exposed to social impoverishment. Repeated reversals of social enrichment to isolation and vice versa led to corresponding changes in sleep patterns, always reflecting the most recent experience. Whole-brain estimations of neurotransmitter levels showed that long-sleeping flies had three times more dopamine than short sleepers. The sleep decrease induced by social isolation was completely blocked when dopaminergic transmission was excessively up- or downregulated, indicating that normal levels of dopamine are required for this kind of behavioral plasticity [39]. To assess the underlying mechanisms of experience-dependent changes in sleep need, the researchers screened mutations in 49 genes associated with learning and memory. Post-impoverishment sleep decrease was blocked by 17 of these mutations, including those affecting the genes *dunce* and *rutabaga*, which have opposite effects on intracellular levels of cyclic adenosine monophosphate (cAMP) [39].

Very recently, Jeffrey Donlea, Paul Shaw, and collaborators published breakthrough evidence that sleep may either downscale or upscale synapses, depending on the experimental conditions [26]. Expression in specific *Drosophila* neurons of the temperature-gated nonspecific cation channel Transient receptor potential cation channel (UAS-TrpA1) allowed the experimenters to induce sleep simply by raising the ambient temperature from 25°C to 31°C. The capacity to induce sleep on demand provided an opportunity to go beyond the correlative studies towards causal links because it made possible the investigation not only of the detrimental effects of the lack of sleep but also of the positive cognitive effects produced by increased sleep. In one set of experiments aimed at testing SHY, fruit flies were subjected to social enrichment or isolation for 5 days and then subjected to a long-term memory task. In addition, some groups were subjected to a transient increase in temperature (25°C to 31°C) that elicited sleep. Flies subjected to isolation were capable of establishing long-term memory, but flies subjected to social enrichment and kept at 25°C were not. Since social enrichment caused an enhancement of synaptic terminals, it was hypothesized that the transient induction of sleep following social enrichment should rescue the capacity for long-term memory formation. Indeed, flies briefly exposed to 31°C after social enrichment recovered the capacity for long-term memory formation [26]. Another set of experiments, however,

addressed the possibility that the cognitive role of sleep goes beyond reversing deficits in learning capacity caused by prolonged wakefulness. In this case, sleep was thermally induced immediately after a training protocol that induces short-term but not long-term memory. Remarkably, flies subjected to post-training sleep acquired long-term memory, indicating that sleep is not simply restorative of learning potential but can also constitute a positive driving force shaping learning [26].

Data in line with these findings have come from a very different topic of investigation, namely development. Studies of rats subjected to early-life REM deprivation showed a role for this state in the maturation of thalamic, cortical, and hippocampal circuits, with a decrease in the stability of long-term potentiation [66, 112–115]. An important developmental effect of sleep has been particularly well demonstrated with regard to ocular dominance columns in the visual cortex [2, 33]. By reversibly inactivating the visual cortex of sleeping cats after a period of monocular deprivation, Frank and collaborators sought to investigate the role of cortical activity in sleep-dependent plasticity. Optical imaging of intrinsic cortical signals and electrophysiological recordings showed that ocular dominance plasticity was significantly decreased when the visual cortices were inactivated during sleep [2, 33]. In a follow-up study, the researchers probed the role of NMDA receptors and calcium-dependent kinases. They found that plasticity was blocked by the intracortical infusion, during post-monocular deprivation sleep, of an antagonist of the NMDA receptor or of an inhibitor of the cAMP-dependent protein kinase (PKA) [2, 33]. They also verified that cats subjected to monocular deprivation and then allowed to sleep showed increased phosphorylation of the extracellular-signal-regulated kinase (ERK), CaMKII, and the GluR1 subunit of the AMPA receptor. These increases in the phosphorylation of LTP-related kinases and an AMPA receptor subunit, all downstream of NMDA receptor/PKA activation, were not observed in cats unexposed to monocular deprivation or not allowed to sleep [2, 33].

A developmental role for sleep has also been discovered in invertebrates. Flies exposed to acute sleep deprivation on their first day of life showed long-lasting deficits in short-term memory [111]. These deficits were reversed by dopamine agonists, and the blockade of the dDA1 receptor in sleep-deprived animals during their critical developmental window prevented subsequent adult learning impairments [111].

A deeper understanding of the molecular consequences of post-learning sleep came from a study conducted by Romcy-Pereira and collaborators [106]. The researchers were interested in the activation of secondary genes related to local changes in synaptic strength and memory stabilization during sleep, after the initial wave of IEG induction.

To this end, they assessed the hippocampal and cortical expression of plasticity-related genes at a late time with respect to the induction of zif-268 expression. Rats underwent uni-hemispheric LTP in the hippocampus and were then separated in waking versus REM groups, according to the behaviors allowed to occur in the post-LTP period. Eighty minutes after displaying a long REM episode (or an equivalent amount of waking time in the control group), the animals were killed, the hippocampi and prefrontal cortices were dissected, and the samples were processed for gene microarray hybridization. The microarray analysis identified a total of 28 upregulated genes, with 13 genes upregulated by REM regardless of prior potentiation, 4 genes with increased levels in the potentiated hemisphere irrespective of behavioral state, and 11 genes selectively upregulated in the potentiated hemisphere of REM animals [106]. Confirmation essays with quantitative real-time PCR analysis in the LTP hippocampus of sleep animals demonstrated an upregulation of the transcription factor albumin D-site-binding protein, which modulates neuronal excitability and ERK expression in the hippocampus [110]. A trend for upregulation of the protein kinase CaMKI, which is involved with activity-dependent dendritic remodeling, was also observed. In the prefrontal cortex, the researchers found a significant LTP/sleep-dependent decrease of GluR1 and spinophilin transcripts, which encode for a subunit of AMPA receptors and a protein phosphatase-1 interacting protein, both highly enriched in dendritic spines and required for synaptic remodeling [1, 72]. Overall, the results indicate that different plasticity-related genes are up- and down-regulated by sleep after the initial IEG response, pointing to complex changes in gene expression related to dendritic reshaping [106].

To which extent is post-learning sleep determinant of experience-dependent synaptic upscaling? Light on this question was shed by Ted Abel's laboratory. The researchers began by determining the cognitive effects of sleep deprivation for 5 h after training for contextual and cued fear conditioning, the former dependent and the latter independent of the hippocampus. Cued fear conditioning was insensitive to both sleep deprivation schedules. Contextual fear conditioning, however, was dependent on post-learning sleep for consolidation. Sleep deprivation from 0–5 h after training decreased performance on contextual fear conditioning, while sleep deprivation from 5–10 h after training did not impair learning [43]. The same research team went on to show that the detrimental effects of sleep deprivation on contextual fear conditioning were caused by a disruption of synaptic plasticity that depends on the cAMP/PKA pathway [134]. The experiments involved a 5-h period of sleep deprivation followed by *in vitro* electrophysiological recordings and stimulation of hippocampal slices of animals pre-exposed (or not) to contextual fear conditioning. Various forms of

NMDA receptor-dependent LTP involving different molecular mechanisms were investigated. Two of these LTP forms, both dependent on cAMP, PKA, transcription, and translation, were impaired in hippocampal slices from sleep-deprived mice. Sleep did not affect two other forms of LTP that are independent of cAMP/PKA signaling. Since one of these is dependent on translation, the authors concluded that brief sleep deprivation must impair synaptic plasticity at a biochemical level prior to translation. Pharmacological and biochemical assays showed that sleep deprivation limits the ability of hippocampal neurons to undergo adenylate cyclase activation. In particular, sleep deprivation decreases CREB phosphorylation that requires cAMP signaling and is required for zif-268 transcriptional regulation. The researchers focused on a good candidate for being responsible for the effects: cyclic nucleotide phosphodiesterases (PDE), the enzymes in charge of cAMP degradation [55]. Further experiments showed that PDE inhibitors were able to rescue cAMP-dependent plasticity and cAMP levels in slices from sleep-deprived mice. PDE-specific cAMP breakdown was increased in sleep-deprived mice, and *in vivo* PDE inhibition rescued the deficit in context-specific memory induced by sleep deprivation [43, 134].

Until these groundbreaking experiments, the cognitive impairment caused by sleep deprivation could only be rescued by sleep itself. The results demonstrate that the synaptic plasticity and memory deficits elicited by sleep deprivation can be rescued with a PDE inhibitor. In sum, the results demonstrate that sustained waking disrupts hippocampal function via a reduction in cAMP signaling caused by an increase in the levels of PDE. By the same token, sleep decreases PDE levels and therefore promotes an increase in cAMP, thus leading to synaptic potentiation.

Sleep-dependent synaptic embossing accounts well for the available data

Can synaptic downscaling linked to passive quiescence really explain the cognitive role of sleep, or is there a theoretical need for active upscaling mechanisms? The current mainstream theory sustains that sleep benefits learning by promoting global synaptic downscaling, able in principle to restore homeostatic balance and enable further waking potentiation [126]. This theory embodies a revival of the passive view of sleep function, which was dominant before the discovery of REM. It focuses exclusively on SWS and finds no place for experience-dependent changes during sleep. In contrast, the contender theory considers sleep as a combination of passive and

active mechanisms, distinguishes the contributions of SWS and REM, and stresses the need to compare sleep with and without prior learning [23, 102]. This synaptic embossing theory proposes that sleep facilitates learning because of the cooperative interaction of its two major states: While SWS reverberates memories in the absence of sensory interference, REM triggers plasticity-related metabolic cascades in selected neuronal networks previously activated during waking and engaged in mnemonic reverberation during SWS [23, 102]. It follows from this view that sleep influences synaptic plasticity bidirectionally, simultaneously promoting synaptic down and upscaling in separate neuronal networks. Such a process would lead to experience-dependent differential plasticity (or simply “synaptic embossing”), with non-Hebbian generalized synaptic downscaling in the background and Hebbian upscaling of selected synapses in the foreground.

More experimentation is necessary to convincingly refute either theory. At the 2009 meeting of the Society for Neuroscience, our group presented novel molecular, electrophysiological, and computational results that corroborate the synaptic embossing theory (manuscripts in preparation). We reported an increase in the phosphorylation of CaMKII during REM that follows novel object exploration [91]. We also showed that post-novelty increases in sleep firing rates affect the same neurons that were activated by novel stimulation during precedent waking experience [28]. Finally, a computer simulation of synaptic weight changes across the sleep–wake cycle using real neuronal data as inputs revealed that REM leads to an increase in synaptic weights in comparison with SWS, due to the higher firing rates of REM [3]. In this computer simulation, the addition during REM of experience-dependent gene expression able to promote long-term synaptic upscaling leads to a marked redistribution of synaptic weights over time. This effect is stochastic in the sense that it depends on the random fluctuations of the synaptic weights at the SWS/REM boundary. The results seem to implement mechanistically the concept of “stochastic resonance” [38, 73] during REM, which has been postulated to form new mnemonic associations and to promote consolidation at synapses activated during prior SWS [24].

Many intriguing questions about the mechanisms of sleep-dependent plasticity remain completely or partially unanswered. What is the exact role played by dopamine? Is acetylcholine, highly abundant during REM, also involved? What is the role of cortisol? What kind of neuronal and local field potential activity is necessary to trigger or deactivate the cAMP/PKA pathway during sleep? How are synapses tagged by waking experience for subsequent sleep plasticity? What is the contribution of these mechanisms for the displacement of memory traces across hippocampocortical circuits?

Above and beyond the many open questions and the present divergence regarding sleep-dependent plasticity, it is clear that synaptic upscaling and downscaling are not mutually exclusive. Experience-dependent synaptic upscaling is compatible with global synaptic downscaling, as long as the two processes occur in separate neuronal networks [102]. Synaptic downscaling during SWS is most surely crucial for learning, but if it were to occur with equal strength in activated and non-activated networks, it would lead to generalized forgetting, not specific learning. I have previously proposed that the combination of synaptic upscaling in selected networks and synaptic downscaling in non-selected networks should greatly increase the signal-to-noise ratio of sleep-dependent memory consolidation [94]. Such differential upscaling of synaptic weights seems apt to carve high-relief memory traces over a background of downscaled synapses, leading to the concept of synaptic embossing. A comparison of stimulated and non-stimulated cortical areas related to different sensory modalities indicates that this is indeed the case [104]. The *Drosophila* data recently published by Donlea and collaborators show that sleep not only restores the capacity for learning but also enhances the duration of memories, a positive effect that can only be explained with some kind of absolute or relative synaptic upscaling [26].

One necessary consequence of the embossing theory is that the net change in synaptic strength during sleep is related to the encoding strength of the preceding waking experience, i.e., by how much synaptic change resulted from the encoding conditions. Context fear conditioning, for instance, is a single trial training paradigm that involves painful, very salient stimuli. As a consequence, context fear conditioning probably determines a great deal of synaptic upscaling during encoding, which is likely to cause major synaptic upscaling during subsequent sleep [43, 134]. It follows from this line of reasoning that different training paradigms will be associated with distinct net balances of synaptic up- and downscaling during subsequent sleep.

The coming years should witness the sleep and memory fields finally agree on the issue of plasticity. Most likely, it will be a convergence on the middle road. Synaptic embossing is the most parsimonious explanation for sleep’s striking ability to consolidate relevant memories while at the same time leading to the forgetting of irrelevant ones, so as to recover the capacity for new learning. The best explanation for the cognitive role of sleep is neither synaptic downscaling nor upscaling exclusively but rather the concerted action of both.

Acknowledgments I thank Jan Born, Rodrigo Romcy-Pereira, and an anonymous reviewer for critical reviews of the manuscript, which helped to balance and increase the depth of the material covered.

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