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Sleep and synaptic homeostasis: a hypothesis

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Abstract

During much of sleep, the cerebral cortex is rippled by slow waves, which appear in the electroencephalogram as oscillations between 0.5 and 4.5 Hz. Slow waves are regulated as a function of previous wakefulness, being maximal at the beginning of sleep and then progressively returning to a baseline level. This paper discusses a hypothesis about the significance of slow-wave activity and its homeostatic regulation. The hypothesis is as follows:

1. Wakefulness is associated with synaptic potentiation in several cortical circuits;
2. Synaptic potentiation is tied to the homeostatic regulation of slow-wave activity;
3. Slow-wave activity is associated with synaptic downscaling;
4. Synaptic downscaling is tied to the beneficial effects of sleep on performance.

The hypothesized link between sleep and synaptic homeostasis is supported by several lines of evidence and leads to testable predictions.

Keywords: Long-term depression; Synaptic scaling; Learning; Consolidation; Delta sleep; Slow waves; Slow oscillation

1. Introduction

During much of sleep, neurons in the cerebral cortex fire and stop firing together in waves of activity having frequencies of less than 4.5 Hz. Such slow-wave activity, which is the most pronounced electroencephalographic (EEG) feature of non-rapid eye movement (NREM) sleep, is also a reliable predictor of sleep intensity. An important feature of slow-wave activity during sleep is that it increases as a function of previous wakefulness, and it gradually decreases in the course of sleep [6]. This homeostatic regulation suggests that slow-wave activity may be linked to some restorative aspect of sleep. However, the mechanisms and functions of slow-wave homeostasis are still unclear. Here we discuss a hypothesis that links sleep with synaptic homeostasis. The hypothesis is as follows:

1. Wakefulness is associated with synaptic potentiation in several cortical circuits;
2. Synaptic potentiation is tied to the homeostatic regulation of slow-wave activity;
3. Slow-wave activity is associated with synaptic downscaling;
4. Synaptic downscaling is tied to the beneficial effects of sleep on performance.

We discuss each of its four points in sequence.

2. Wakefulness and synaptic potentiation

During wakefulness, when animals explore novel situations, attend to their surroundings, react to sensory stimuli, perform motor tasks, think, make associations, and are punished or rewarded, they learn about their environment. Underlying learning are long-lasting changes in the strength or number of synaptic connections between neurons, which are mediated by complicated cascades of cellular events. Among the best documented molecular correlates of learning are the phosphorylation of transcription factors such as CREB and the induction of certain plasticity-related genes such as *Arc*, *BDNF*, and *NGFI-A* (e.g. [43,55]). The induction of these cellular correlates of memory acquisition were first demonstrated in long-term potentiation (LTP) paradigms using high frequency electrical stimulation of cerebral white

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matter. Later studies have shown that molecular correlates of LTP can be induced in specific brain regions using behavioral learning paradigms [43].

Remarkably, cellular correlates of LTP are also expressed in many brain regions during spontaneous wakefulness, when animals are left undisturbed in their cages and are free to engage in their preferred activities. This "spontaneous" induction of LTP-related genes can increase further if the environment is more stimulating and rich in novel objects. On the other hand, the expression of LTP-related genes is severely reduced or abolished during sleep [14]. This observation suggests that spontaneous wakefulness, even for a rat in a confined and familiar environment, is inevitably associated with some LTP-related molecular changes, while sleep is not [48].

From an evolutionary perspective, it makes sense that the potentiation of neural circuits should occur during wakefulness, when an animal is active and exposed to the environment, and not during sleep, when neural activity is unrelated to external events [48]. However, given that spontaneous mean firing rates of cortical neurons in wakefulness and sleep are comparable, how is the induction of LTP-related genes restricted to wakefulness [46]? One reason may be that sensory, motor, or cognitive activities that occur during active wakefulness are often associated with high peak firing rates, which are likely to give rise to LTP-related plastic changes [45]. Another reason is that the firing of the noradrenergic system is high during wakefulness, especially during salient events, while it is very low or absent during sleep [3]. If the noradrenergic innervation of the cerebral cortex is destroyed, P-CREB, Arc, BDNF and NGFI-A decrease towards the levels seen in sleep even if the animal is awake and behaving, and even if the waking electroencephalographic (EEG) is essentially unchanged [12,14]. Consistent with these observations, noradrenergic lesions impair at least some forms of learning [40].

Based on this evidence, the first part of the hypothesis states that wakefulness is generally accompanied by LTP-like changes in the brain, whether or not an animal is specifically engaged in experimental learning paradigms or is simply spontaneously active. This statement implies that plastic changes at the synaptic level can occur in the absence of behavioral changes commonly used to index the occurence of learning. After all, synapses and neurons do not know whether they are engaged in a learning paradigm, but only whether strong presynatpic firing is followed by postsynaptic depolarization in the presence of appropriate levels of neuromodulators.

The hypothesis also asserts that the potentiation of neural circuits occuring during wakefulness results in a net increase in synaptic weight impinging onto cortical neurons. This assertion implies that, at least in the cerebral cortex, plastic changes occuring during wakefulness result in a systematic imbalance between synaptic potentiation and depression. While direct evidence supporting this assertion is scant, it is likely that the diffuse induction of LTP-like molecular changes during wakefulness reflects a net potentiation of synaptic inputs onto cortical neurons [54]. Moreover, unit recordings show that, on a background of low spontaneous activity, the cerebral cortex engages in sensory, motor, or cognitive tasks by having select groups of neurons strongly increase, rather than decrease, their firing rate. This predominantly positive signaling at the level of neural activity would seem to imply, when it comes to plasticity, an imbalance towards potentiation. Less indirect evidence comes from anatomical work reporting a net and diffuse increase in synaptic density in animals exposed to enriched environments likely to induce LTP-like molecular changes [32]. Finally, at least one study has directly demonstrated that stimulating a whisker for 24 h produces a selective net increase of synaptic density (by 35%) on cortical neurons in the corresponding barrel field [33].

3. Synaptic potentiation and slow-wave homeostasis

One of the best established facts in sleep regulation in mammals is that slow-wave activity increases in proportion to the duration of prior wakefulness and progressively decreases during sleep [5]. The present hypothesis states that the homeostatic regulation of slow-wave activity is tied to the amount of synaptic potentiation that has occured during previous wakefulness. Specifically, the higher the amount of synaptic potentiation in cortical circuits during wakefulness, the higher the increase in slow-wave activity during subsequent sleep.

This portion of the hypothesis relies on some preliminary evidence from both animals and humans. For example, a direct prediction of the hypothesis is that, if wakefulness is not accompanied by LTP-like changes in synaptic strength, the homeostatic increase in slow-wave activity after wakefulness should be eliminated. This prediction was tested by examining animals with a lesioned noradrenergic system, which have a greatly reduced expression of LTP-related molecules in the cerebral cortex after periods of wakefulness [12,14]. Although in these animals the amount and timing of sleep are unchanged, results from our laboratory indicate the disappearance of the peak in slow-wave activity that is normally seen in the morning hours after the nocturnal activity phase. Thus, it may be that it is not wakefulness as such, but the induction of LTP-related molecules normally associated with wakefulness, which is responsible for driving the homeostatic increase in slow-wave activity. Further studies are in progress to establish whether noradrenaline lesioned animals have a blunted slow-wave response to sleep deprivation, and whether similar effects are obtained by interfering with the expression of LTP-related molecular changes using constitutive or inducible genetic manipulations of key players in the LTP cascade. Another, related prediction of the hypothesis is that there should be a relationship between the kind of activities animals are engaged in during wakefulness, the corresponding level of induction of LTP-related

genes [30], and the amount of slow-wave activity during subsequent sleep [37].

Molecular correlates of LTP or of learning in humans are of course not available. However, it is likely that when we actively engage in various waking tasks, strong synaptic activation is accompanied by cellular and molecular changes similar to those occuring in other mammals. A key prediction of the hypothesis is that, to the extent that synaptic potentiation is particularly strong in specific brain areas, slow-wave activity during subsequent sleep should increase disproportionately in that area—a kind of local intensification of sleep. Local differences in slow-wave homeostasis have been described in both humans and rodents, with frontal regions showing an especially strong response to sleep deprivation [20,28]. Since frontal regions are especially susceptible to the effects of sleep deprivation, and may be working harder than other brain areas during wakefulness, a possible relationship to synaptic potentiation is at least conceivable [26]. Direct evidence linking brain activation with local sleep homeostasis has been sought in two studies employing a lateralized task, one in humans [29] and one in rats [52]. Both studies found a slight asymmetry in power between the two sides after the lateralized task, but the magnitude of the effect was fairly small. In the human study, this may have been due to the use of passive vibration of the hand, which is probably a much less potent stimulus for circuit potentiation than an active task.

Most recently, we have searched for signs of local slow-wave homeostasis using high density EEG and a visuomotor task [23] that actively engages a subject's attention (Huber et al., unpublished results). This visuomotor task, which involve rapidly and accurately moving a cursor to hit a visually presented target, is known to strongly activate neural circuits in parietal and motor areas [23]. We reasoned that, if such strong activation is associated with the induction of LTP-related molecular changes, and if the latter is tied to slow-wave homeostasis, there should be an increase in slow waves during the sleep episode subsequent to the tasks. Furthermore, such increase should be localized to the appropriate brain regions. Preliminary results obtained using high density EEG are in accord with both predictions, showing a substantial, localized increase of slow-wave activity in parietal cortex during sleep after the visuomotor task, compared to sleep after a visual control condition. Further changes were observed in motor and parietal areas when comparing the visuomotor task with a kinematically equivalent task where, unbeknownst to them, subjects had to adapt to a systematic rotation of their trajectories [23,34]. Thus, the presumed induction of local plastic changes associated with practicing a visuomotor task is associated with a local induction of slow-wave activity in subsequent sleep.

What could be the mechanism linking local synaptic potentiation during wakefulness with increased slow waves during sleep? A straightforward explanation could be that the amount of slow waves recordable via EEG reflects the overall strength of corticocortical synapses, and thereby represents a direct reflection of the amount of potentiation. Evidence that the amplitude of synchronized activity is heavily influenced by the amount and efficacy of synaptic transmission comes both from experimental [2] and modeling work [4,16]. Moreover, slow-wave activity changes during the lifespan in a way that seems to follow cortical synaptic density [18]. Also, after visual deprivation during the critical period—a procedure associated with synaptic depression [25], slow waves are reduced by 40% in the absence of changes in sleep architecture [39]. Finally, according to recent studies, the increase in power after wakefulness extends to other frequency bands besides the slow wave or delta band [1,7–10,27], which would be consistent with a generalized increase in neural synchronization due to increased synaptic strength.

Other local mechanisms could also contribute to tying the amplitude of slow oscillations to the extent of synaptic potentiation during wakefulness. Underlying slow-wave activity in the EEG is a slow oscillation of the membrane potential of cortical cells [46]. The slow oscillation comprises a depolarized up-phase, during which neurons fire at relatively high rates, followed by a hyperpolarized down-phase, during which neurons are silent. The down-phase is probably brought about by a sodium-dependent potassium current that is activated as a function of neuronal firing. According to modeling studies, a net potentiation of synaptic inputs causes a stronger activation of the sodium-dependent potassium current, which leads in turn to a longer and more hyperpolarized down-phase, and thus to slow oscillations of increased amplitude (Hill and Tononi, unpublished results).

4. Slow-wave homeostasis and synaptic downscaling

We have assumed that LTP-related changes occuring in the cortex during wakefulness lead to a net increase in synaptic weight onto neurons, and that such increase is reflected in an increased slow-wave activity. Is such slow-wave activity a mere epiphenomenon, or does it have some functional significance? According to the hypothesis, slow waves occuring in the cortex during sleep would actively promote a generalized depression or downscaling of synapses. In this way, the total synaptic weight to neurons would progressively return to a baseline level, thus effecting a kind of synaptic homeostasis. Correspondingly, since the amplitude of slow waves would be tied to total synaptic weight, power in the delta band would progressively return to a baseline level, consistent with slow-wave homeostasis.

A need to rescale synaptic weight after learning, in order to preserve a constant level of synaptic input without obliterating memory traces, confer stability to neuronal firing, and prevent runaway potentiation or depression, has long been recognized in computational models of synaptic plasticity (e.g. [38]). Mathematically, rescaling of the synapses impinging on the same neuron is easily achieved either by

subtracting the same amount of synaptic weight from all synapses, or by subtracting an amount proportional to the strength of each synapse, i.e. dividing each weight by the same factor. Recently, a process of this kind has been shown to occur in vitro and in vivo in neocortical cells [17,49]. In these experiments, blocking or reducing neural activity induces a proportional increase in the strength of all synapses impinging on a neuron, while increasing neural activity does the opposite. Since the net effect is to make silent cells more excitable and hyperactive cells less excitable, the process has been called activity-dependent synaptic scaling, and it is assumed to serve synaptic homeostasis.

Unlike activity-dependent synaptic scaling, which can go in both directions, we are assuming here that slow-wave activity would only achieve downscaling. Moreover, we are assuming that what is regulated is not so much neuronal firing, but total synaptic weight. Nevertheless, like activity-dependent synaptic scaling, downscaling during slow-wave activity would affect most or all of a neuron's synapses. In this respect, downscaling is conceptually different from long-term depression (LTD), which affects select groups of synapses, or depotentiation, which affects only recently potentiated ones [31]. Since downscaling would affect all synapses in a similar manner, it would not require any fine-tuning at the level of the individual synapse. By contrast, selective potentiation or depression of specific synapses would require carefully titrated synaptic activations, which would not be easy to achieve considering that neural activity during sleep is by and large intrinsically generated. Despite these differences, we hypothesize that downscaling is likely to use many of the same molecular mechanisms involved in depression/depotentiation and activity-dependent scaling. Substantial evidence indicates that these forms of plasticity depend on the dephosphorylation and subsequent internalization of AMPA receptors that ultimately leads to a reduction in synaptic efficacy [35,50]. Whichever the specific mechanism, the hypothesis is that a generalized synaptic downscaling during sleep ensures the maintenance of balanced synaptic input to cortical neurons. Thus, the homeostasis of sleep and slow waves would both effect and reflect the homeostasis of synapses [48].

This part of the hypothesis relies on several considerations. As we have seen, the fundamental cellular phenomenon underlying non-rapid eye movement (NREM) sleep is the slow oscillation, which is thought to organize slow-wave activity in the cortex, and which is seen in virtually every cortical cell recorded intracellularly [46]. The slow oscillation occurs at a frequency that is ideally suited to induce depotentiation/depression in stimulation paradigms, namely <1 Hz [31]. Thus, from a frequency perspective alone, slow-wave sleep would be a good candidate for promoting depotentiation/depression.

Several factors could explain why low frequency activity during sleep might promote depression. For example, changes in calcium dynamics, which are crucial for depression [31], are likely to occur during slow waves. The unique neuromodulatory milieu of NREM sleep—low acetylcholine, noradrenaline, serotonin, and histamine—may also be important, as well as the fact that depression is prevented by BDNF, which is low in sleep [42]. The most significant factor promoting downscaling, however, could be the very sequence of depolarization (up-phase) and hyperpolarization (down-phase) that characterizes slow oscillations at the cellular level [46]. The close temporal pairing between generalized spiking at the end of the up-phase and generalized hyperpolarization at the beginning of the down-phase may indicate to synapses that presynaptic input was not effective in driving postsynaptic activity, a key requirement for depression [31]. Moreover, an appealing feature of this entire process is that it could be self-limiting. This would be the case if the reduction of slow-wave activity observed macroscopically in the EEG were to correspond to a reduction of slow oscillations at the single cell level, and thus to a reduction of downscaling. For example, the progressive reduction of synaptic strength due to downscaling would reduce postsynaptic depolarization, an effect further amplified by the reduced synchronization of slow oscillations among different cells. As a consequence, sodium-dependent potassium currents that bring about the hyperpolarized phase would be progressively less activated. Eventually, cortical cells would stop alternating between crisp up- and down-phases, and hover instead around an intermediate membrane potential inadequate for downscaling.

A role for NREM sleep in downscaling is also compatible with recent molecular evidence. We have seen that during NREM sleep the expression of LTP-related molecules reaches a low level [14]. A nearly exhaustive screening of gene expression in sleeping and awake rats indicates that NREM sleep may be a time during which molecules implicated in depotentiation/depression are selectively upregulated [11]. Such molecules include calcineurin, a phosphatase that dephosphorylates AMPA receptors potentiated during LTP, protein phosphatase I, calmodulin-dependent kinase IV, glutamate receptor δ2 subunit, FK506 binding protein 12, inositol, 1,4,5-trisphosphate receptor, amphiphysin II, and several proteins involved in vesicle recycling. Also, NREM sleep is associated with higher levels of insulin [44], which promotes the internalization of AMPA receptors and LTD [36]. Thus, at least at the molecular level, sleep may not just be unfavorable to synaptic potentiation, but specifically conducive to generalized synaptic depotentiation/depression. More direct tests of this prediction can be envisaged. It is already known that sleep altogether favors dephosphorylation in the brain [13]. One could further measure phosphorylation levels in sleep and wakefulness of residues of the AMPA channel involved in potentiation/depotentiation and depression/dedepression, as well as indices of AMPA receptor internalization.

Another intriguing indication that NREM sleep may be associated with synaptic downscaling comes from studies of monocular visual deprivation in kittens, a well-known model of cortical plasticity. During a critical period of brain

development, occluding one eye when the animal is awake in the light for 6 h greatly reduces the ability of cortical cells to respond to the occluded eye. It is now thought that such plastic reduction is due to LTD of cortical connections related to the deprived eye [25]. The plastic depression of responses to the occluded eye can be increased if the animal remains awake in the light, but not in the dark, for another 6 h. Remarkably, an equivalent increase in depression can be seen if the animal is allowed to sleep for 6 h in the dark [22]. This result has been interpreted in terms of sleep-mediated "consolidation", but it could as well be due to sleep-related downscaling.

Finally, it can be argued that a process of generalized downscaling may not be compatible with wakefulness, while it would be ideally compatible with sleep, a state during which the brain is both spontaneously active and virtually disconnected from the environment. During sleep, in the depolarized up-phase of the slow oscillation, most or all cortical neurons are spontaneously active [46], so that most synaptic circuits can be activated in an off-line mode without interfering with ongoing behavior. This would obviously not work well during wakefulness. Similarly, the subsequent hyperpolarized down-phase, which would bring about generalized downscaling, does not constitute a problem during sleep. On the other hand, repetitive hyperpolarizations would seriously interfere with behavior if they were to occur during wakefulness. Finally, the reduced activity of the noradrenergic system during sleep would ensure that only downscaling occurs, and not potentiation. Conversely, the occurence of global downscaling might be incompatible with the occurence of synapse-selective potentiation during wakefulness.

5. Synaptic downscaling and performance

The last part of the hypothesis states that active synaptic downscaling occurring during sleep is beneficial for cellular functions and is tied to overnight performance improvement. Undoubtedly, many aspects of behavioral performance improve after sleep and are negatively impacted by sleep deprivation, and it is conceivable that avoiding synaptic overload by maintaining synaptic homeostasis would be beneficial for many cellular processes, such as energy metabolism and membrane maintenance. Here we focus on a beneficial effect of sleep on an aspect of performance that has been well-characterized in several recent studies employing procedural tasks, such as learning to finger-tap in sequence [47]. Specifically, these studies have shown that sleeping after learning the task produces a substantial enhancement in performance, and that the enhancement is specifically tied to sleep and not to circadian time or to the mere passage of time [53]. It is not clear, however, why performance is enhanced by sleep.

According to the hypothesis, a specific case can be made for performance enhancement through an increase in the signal to noise ratios (SNR) at the neuronal level, which would be obtained through synaptic downscaling. To illustrate, let us reconsider the visuomotor task discussed in connection with local slow-wave homeostasis. The neural substrates of many forms of visuomotor learning are thought to be changes in synaptic strength within circuits in motor and parietal areas. PET studies indicate that, during visuomotor learning, brain activation is at first diffuse and bilateral, and only after further practice does it converge upon more restricted foci of cortical activation [23]. This pattern is not surprising, since visuomotor learning is an incremental process, during which early executions are tentative and inaccurate, and only slowly converge upon smooth, correct trajectories. What is noteworthy, however, is that at any given execution, local circuits have no way of knowing which synapses and neurons were contributing to correct or incorrect aspects of the movement. Thus, while synapses contributing to a correct movement will become progressively more efficacious (signal), other synapses contributing to erroneous or imperfect movements will also be potentiated (noise).

It is here that synaptic downscaling during sleep can play a role. According to the hypothesis, during sleep the strength of each synapse would decrease by a proportional amount, until the total amount of synaptic weight impinging on each neuron returns to a baseline level. Provided there is a threshold below which synapses become ineffective or silent, synapses contributing to the noise, being on average weaker than those contributing to the signal, would cease to interfere in the execution, and the SNR would increase. More generally, downscaling with a threshold would counteract runaway synaptic potentiation and promote competition, which may be especially important during development. And of course, downscaling would result by definition in homeostasis of total synaptic weight [51]. Given that headroom for increasing the number or strength of synapses is probably severely limited in an adult cortex, synaptic homeostasis would help maintain headroom for plastic changes to occur and avoid saturation. Finally, synaptic homeostasis may prevent other unwelcome imbalances at the cellular level that might result from synaptic overload [11].

While this last part of the hypothesis is speculative, it is not untestable. As was mentioned above, we found that visuomotor practice produces a marked, local increase in slow-wave activity that is localized to the areas where potentiation presumably has taken place [23]. Moreover, sleep after visuomotor learning enhances performance (Huber et al., unpublished results), consistent with previous reports using other learning tasks [47]. If the homeostatic increase in slow waves is important for downscaling, interfering with such slow waves should abolish the sleep-related performance enhancement. This prediction can be tested, for example, by administering acoustic stimuli to selectively disrupt slow waves following rotation adaptation learning [19].

6. Caveats and conclusions

Clearly, many aspects of the hypothesis presented here are bound to be inaccurate, incomplete, or outright wrong. Inaccuracy is guaranteed by the complexity of biological systems. Thus, the suggestion that the key mechanism of downscaling is the internalization of AMPA receptors during the up–down transition of the slow oscillation is undoubtedly simplistic. As an example of incompleteness, the hypothesis assumes that slow-wave activity is locally regulated in the cortex, but it does not discuss what brain mechanisms might be responsible for the regulation of sleep duration. Presumably, slow-wave homeostasis occuring diffusely in most brain circuits would by itself produce increased sleep duration. However, while sleep duration and intensity generally vary together, they can be dissociated, especially in young animals [21]. Are there hypothalamic centers that, above and beyond local slow-wave homeostasis, keep track of the amount of wakefulness as a reliable predictor of the amount of synaptic potentiation, and which regulate sleep duration accordingly? A related issue is the role played by neuromodulators such as acetylcholine in determining the amplitude of slow-wave activity during sleep. Since neuromodulators are released diffusely, they cannot be responsible for local slow-wave homeostasis of the kind seen with the visuomotor task. However, neuromodulators are certainly responsible for blocking slow-wave activity during wakefulness, and at sleep onset their reduced release promotes cellular hyperpolarization and accompanies the emergence of slow waves. If neuromodulatory systems were to tire during wakefulness, the homeostasis of slow waves would reduce to a centrally regulated phenomenon just like the circadian timing of sleep, and it would provide no clue towards the functional role of sleep for cortical cells.

An example of where the hypothesis may be entirely wrong is the following. Studies in slice preparations suggest that cells may maintain an ongoing, rapid balance between LTP and LTD at different synapses [41]. While some amount of LTD is likely to occur during wakefulness, a strong prediction of the hypothesis is that, at least in the adult and in vivo, active wakefulness would be associated with a net increase in the synaptic weight impinging on many cortical neurons, and that sleep would be needed to redress the balance. As was mentioned above, one study has directly demonstrated a net increase in synaptic density in a cortical barrel field after 24 h of whisker stimulation. Interestingly, the same study reports that, 4 days later, synaptic density had returned to its baseline level [33]. The hypothesis would predict that such return to baseline is sleep-dependent. This prediction could also be tested in humans by recording cortical EEG potentials evoked by transcranial magnetic stimulation (TMS). According to the hypothesis, the amplitude of TMS-evoked potentials on the scalp should be higher at the end of a day of wakefulness and lower after a night of sleep. Furthermore, TMS responses should increase selectively in brain areas where local slow-wave homeostasis has been induced, for example, with the visuomotor task discussed above.

Finally, the hypothesis triggers some further questions. For example, can anesthetic agents also produce synaptic downscaling, to the extent that they promote slow-wave activity comparable to that of NREM sleep? Is the rebound in slow-wave activity observed after torpor or hibernation due to previous synaptic potentiation? Does declarative learning also rely on synaptic downscaling during sleep? How does the hypothesis apply to other brain structures where sleep rhythms are different, such as the hippocampus? Or to other species, such as the fruit fly? And finally, what about REM sleep? Could it be, for example, that with its steady depolarization and high spontaneous activity, REM sleep might promote the insertion of AMPA receptors in the synaptic sites that are still effective after the downscaling of NREM sleep, and thereby favor their consolidation? Such “polishing” of synapses after the “cleansing” action of NREM sleep would agree with the regular alternation between NREM and REM sleep (cf. [24]) and the reported cooperativity between the two stages of sleep in certain procedural tasks [47]. Moreover, it would agree with the important role played by spontaneous activity in the development of neural connectivity [15]. Alternatively, given that intense spontaneous activity can lead to the cleansing of uncorrelated synapses and to the relative consolidation of correlated ones [15,56], REM sleep could be achieving, with different means, an effect partly similar to the one postulated here for NREM sleep.

Clearly, it would be premature to speculate further at this stage. Yet, while the hypothesis discussed above stands a great chance of being wrong, it is perhaps useful in tying together events at the cellular level with macroscopic electrical phenomena and with their behavioral consequences. Furthermore, the four points it makes are experimentally testable.

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