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Sleep function and synaptic homeostasis

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Summary
This paper reviews a novel hypothesis about the functions of slow wave sleep—the synaptic homeostasis hypothesis. According to the hypothesis, plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain circuits. The role of sleep is to downscale synaptic strength to a baseline level that is energetically sustainable, makes efficient use of gray matter space, and is beneficial for learning and memory. Thus, sleep is the price we have to pay for plasticity, and its goal is the homeostatic regulation of the total synaptic weight impinging on neurons. The hypothesis accounts for a large number of experimental facts, makes several specific predictions, and has implications for both sleep and mood disorders.

Introduction
This paper discusses a novel hypothesis—the synaptic homeostasis hypothesis—which claims that sleep plays a role in the regulation of synaptic weight in the brain. The synaptic homeostasis hypothesis can account for several aspects of sleep and its regulation, and makes several specific predictions. In brief, 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 neural function and, indirectly, on performance.

A useful way of introducing the synaptic homeostasis hypothesis is to relate it to one of the best-established models of sleep regulation—the two-process model. The model distinguishes between the circadian and the homeostatic regulation of sleep propensity. The circadian component (Process C) describes how sleep propensity changes during the 24 h. Process C is well understood, both in its mechanisms, centered in the suprachiasmatic nucleus, and in its function, which is to restrict sleep to a time of day that is ecologically appropriate. The homeostatic component (Process S) accumulates exponentially during wakefulness and is discharged when we sleep, also exponentially but with a faster time course (Fig. 1). The time course of Process S was derived from a physiological variable, EEG slow-wave activity (SWA) in the electroencephalogram (EEG) of non rapid eye movement (NREM) sleep. The homeostatic regulation of SWA suggests that it may reflect some restorative aspect of sleep, but what this aspect may be remains unknown.

According to the present hypothesis, Process S describes the process of synaptic homeostasis.
Specifically, the curve in Fig. 1 can be interpreted as reflecting how the total amount of synaptic strength in the cerebral cortex (and possibly other brain structures) changes as a function of wakefulness and sleep. Thus, the hypothesis claims that, under normal conditions, total synaptic strength increases during wakefulness and reaches a maximum just before going to sleep. Then, as soon as sleep ensues, total synaptic strength begins to decrease, and reaches a baseline level by the time sleep ends. In addition to claiming a correspondence between the homeostatic Process S and total synaptic strength, the hypothesis proposes specific mechanisms, whereby synaptic strength would increase during wakefulness and decrease during sleep, and suggests why the tight regulation of synaptic strength would be of great importance for the brain.

**Synaptic homeostasis: a schematic diagram**

The diagram in Fig. 2 presents a simplified version of the main points of the hypothesis. During wakefulness (yellow background), we interact with the environment and acquire information about it. The EEG is activated, and the neuromodulatory milieu (for example, high levels of noradrenaline, NA) favors the storage of information, which occurs largely through long-term potentiation of synaptic strength. This potentiation occurs when the firing of a presynaptic neuron is followed by the depolarization or firing of a postsynaptic neuron, and the neuromodulatory milieu signals the occurrence of salient events. Strengthened synapses are indicated in red, with...
their strength given by a number. Note that one synapse grows to a strength of 150, while another synapse does not change and stays at 100. Note also the appearance of a new synapse with a strength of five. Due to the net increase in synaptic strength, waking plasticity has a cost in terms of energy requirements, space requirements, and progressively saturates our capacity to learn.

When we go to sleep (blue background), we become virtually disconnected from the environment. Changes in the neuromodulatory milieu trigger the occurrence of slow oscillations in membrane potential, comprising depolarized and hyperpolarized phases, which affect every neuron in the cortex, and which are reflected in the EEG as SWA. The changed neuromodulatory milieu (for example, low levels of noradrenaline) ensures that synaptic activity is not followed by synaptic potentiation, which makes adaptive sense given that synaptic activity during sleep is not driven by interactions with the environment. Because average synaptic strength at the end of the waking period is high, neurons undergoing sleep slow oscillations are highly synchronized. As a result, the EEG of early sleep shows slow waves of high amplitude.

The slow waves, however, are not just an epiphenomenon of the increased synaptic strength, but have a role to play. The repeated sequences of depolarization–hyperpolarization cause the downscaling of the synapses impinging on each neuron, which means that they all decrease in strength proportionally, here by 20%. Thus, a synapse that after wakefulness had strength of 100 is downscaled to 80, another synapse, which had been potentiated to 150, is downscaled to 120 (green color). The synapse with a strength of 5, having been downscaled below a minimum strength, has been ‘downselected’ or removed altogether. The reduced synaptic strength reduces the amplitude and synchronization of the slow oscillations in membrane potential, which is reflected in a reduced SWA in the sleep EEG. Because of the dampening of the slow waves, downscaling is progressively reduced, making the process self-limiting when synaptic strength reaches an appropriate baseline level.

Indeed, total synaptic strength, which had increased from 200 (100 + 100) at the beginning of wakefulness to 255 (100 + 150 + 5) at the end of wakefulness, is downscaled back to 200 (120 + 80) by the end of sleep. By returning total synaptic weight to an appropriate baseline level, sleep enforces synaptic homeostasis. This has benefits in terms of energy requirements, space requirements, and learning and memory. Thus, when we wake up, neural circuits do preserve a trace of the previous experiences, but are kept efficient at a recalibrated level of synaptic strength, and the cycle can begin again.

The main claims of the synaptic homeostasis hypothesis

After this schematic depiction of the hypothesis, we now turn to describing its main points in more detail, and to discussing some supporting evidence.

Wakefulness and synaptic potentiation

The synaptic homeostasis hypothesis states that wakefulness is accompanied by synaptic potentiation in a large fraction of cortical circuits, resulting in a net increase in synaptic weight. According to the hypothesis, plastic changes would occur through much of waking life, whenever we are alert and make behavioral choices, whether or not we are specifically engaged in experimental learning paradigms. After all, synapses and neurons do not know whether they are engaged in a learning paradigm, but only whether strong presynaptic firing is accompanied by postsynaptic depolarization or firing in the presence of appropriate levels of neuromodulators, which should be a frequent occurrence during alert wakefulness. Also, according to the hypothesis, plastic changes occurring during wakefulness, at least in the adult, would result more often in long-term potentiation (LTP) than in long-term depression (LTD), thus resulting in a net potentiation of synaptic strength.

Evidence

Direct evidence supporting this part of the hypothesis comes from anatomical work demonstrating a net and diffuse increase in synaptic density in animals exposed to enriched environments likely to induce LTP-like molecular changes. Local increases in synaptic density have also been observed. For example, stimulating a whisker for 24 h produces a selective net increase of synaptic density (by 35%) on cortical neurons in the corresponding barrel field. Strongly suggestive evidence for synaptic potentiation comes from the finding that spontaneous wakefulness is regularly associated with the diffuse induction of molecular changes usually associated with LTP, including the phosphorylation of cAMP–responsive element–binding protein (CREB) and the induction of genes such as Arc, brain-derived neurotrophic factor (BDNF), nerve growth factor–induced gene A (NGFI-A), Homer, and neuronal activity–regulated pentraxin (Narp) (e.g. ). This induction of LTP-related genes during spontaneous
wakefulness can increase further if animals are kept awake longer by gentle handling, or if they engage in extensive exploration of their environment (Huber et al., in preparation). During sleep, by contrast, the expression of LTP-related genes is severely reduced or abolished.\textsuperscript{5,6,10} Support for the notion that synaptic strength may increase during wakefulness also comes from experiments in humans\textsuperscript{11} and mice\textsuperscript{12,27} showing that brain metabolism, which is mostly due to synaptic activity, increases from early to late wakefulness (see below).

**Mechanisms**

From an evolutionary point of view, 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.\textsuperscript{13} However, given that spontaneous mean firing rates of cortical neurons in wakefulness and sleep are comparable,\textsuperscript{14} how is the induction of LTP-related genes restricted to wakefulness? One reason may be that sensory, motor, or cognitive activities that occur during active wakefulness are often associated, in a small subset of neurons, with high peak firing rates that are likely to give rise to LTP-related plastic changes.\textsuperscript{15} Another mechanism could be the state-dependent firing of certain neuromodulatory systems.\textsuperscript{16} For example, the firing of the noradrenergic system is high during wakefulness, especially during salient events, while it is very low or absent during sleep.\textsuperscript{17} Noradrenaline is important for the induction of LTP,\textsuperscript{18} and noradrenergic lesions impair at least some forms of learning.\textsuperscript{19} Indeed, if the noradrenergic innervation of the cerebral cortex is destroyed, \textit{P-CREB}, \textit{Arc}, \textit{BDNF}, \textit{NGFI-A}, \textit{Homer} and \textit{Narp} are down close to the levels seen in sleep even when the animal is awake and behaving, and even if the waking EEG is essentially unchanged.\textsuperscript{5,20} The effect of noradrenaline is specific, since serotonergic lesions have no effect on the expression of such genes.\textsuperscript{21}

**Synaptic potentiation and slow wave homeostasis**

The synaptic homeostasis hypothesis states that the homeostatic regulation of SWA is tied to the amount of synaptic potentiation that has occurred during previous wakefulness. Specifically, the higher the amount of synaptic potentiation in cortical circuits during wakefulness, the higher the increase in SWA during subsequent sleep.

**Evidence**

This portion of the hypothesis relies on evidence from both animal and human studies. Consistent with the hypothesis, increasing the duration of wakefulness by a few hours (by gentle handling) produces an increase in the expression of markers of synaptic potentiation,\textsuperscript{10} followed by an increase in SWA. The level of induction of LTP-related genes\textsuperscript{22} and the amount of SWA during sleep\textsuperscript{23} should depend not just on the duration, but also on the quality of wakefulness. Indeed, recent experiments have shown that, for the same duration of wakefulness, if animals spend more time exploring their environment, markers of synaptic potentiation are further upregulated, and SWA during subsequent sleep is further increased (Huber et al., in preparation). On the other hand, if wakefulness is not accompanied by LTP-like changes in synaptic strength, the homeostatic increase in SWA should be eliminated. This prediction was confirmed 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.\textsuperscript{5,20} Although in these animals the amount and timing of sleep were unchanged, the peak in SWA that is normally seen in the morning hours after the nocturnal activity phase was markedly dampened, and so was the SWA response to sleep deprivation.\textsuperscript{112} Thus, the hypothesis suggests that it is not wakefulness as such, but the induction of LTP-related molecules normally associated with wakefulness, that is responsible for driving the homeostatic increase in SWA.

An intriguing prediction of the hypothesis is that, to the extent that synaptic potentiation is particularly strong in specific brain areas, SWA during subsequent sleep should increase disproportionately in that area—a kind of \textit{local} intensification of sleep. We have searched for signs of local slow wave homeostasis using high definition EEG to investigate sleep after learning a visuomotor task.\textsuperscript{24} In this task, performed shortly before bedtime, subjects reached for visual targets using a handheld cursor while unconsciously adapting to systematic rotations imposed to the perceived cursor trajectory.\textsuperscript{25} One week earlier or later, subjects performed a control task that was subjectively indistinguishable and kinematically identical, but in which the cursor trajectory was not rotated. Thus, the only difference between the two tasks was that the rotation adaptation task involved (implicit) learning of a compensatory rotation, presumably mediated by synaptic potentiation in specific brain areas, whereas the control task did not. Indeed, previous PET work had shown that rotation learning involves a circumscribed
region in right parietal cortex. As predicted by the hypothesis, when we compared rotation adaptation to control tasks, we found a local increase of SWA (27%) extending over a small cluster of electrodes. Thus, the presumed induction of local plastic changes associated with practicing a visuomotor task is associated with a local induction of SWA in subsequent sleep. The increase in power was mostly in the slow wave frequency range, and it declined over time, just like the global homeostatic response of SWA. Moreover, the increase of SWA was localized exactly at the predicted spot in right parietal cortex. These new results are in line with previous evidence for local SWA homeostasis in humans and rats, and fit as well with other proposals suggesting that sleep may be regulated locally.

Well-documented topographic differences in slow wave homeostasis, with frontal regions showing an especially strong response to sleep deprivation, may also be related to topographic differences in the susceptibility to plastic changes.

Evidence for a relationship between synaptic strength or density and SWA also comes from developmental studies. SWA changes during the lifespan in a way that seems to follow cortical synaptic density, as indicated directly by electron microscopy on post-mortem tissue and by MRI estimates of the amount of gray matter. Thus, both synaptic density and SWA reach a peak in adolescence, after which they decline rapidly, and continue a slower decline into old age. Pathological decreases in synaptic density, as observed in neurodegenerative disorders and schizophrenia, are also associated with reductions in SWA. Moreover, after visual deprivation during the critical period—a procedure associated with synaptic depression, slow waves are reduced by 40% in the absence of changes in sleep architecture.

Mechanisms
What could be the mechanism linking local synaptic potentiation during wakefulness with increased slow waves during sleep? Underlying the SWA recorded in the EEG are oscillations in neuronal membrane potential, the most important of which is a slow oscillation that is generated by cortical cells and synchronized by cortico-cortical connections. 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, stronger cortico-cortical connections cause 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. Furthermore, stronger cortico-cortical connections increase the degree of synchronization among populations of neurons. Both effects, the increased amplitude of the slow oscillation of individual cells, and the increased synchronization of slow oscillations among populations of cells, are reflected in slow waves of larger amplitude at the EEG level. Increased neuronal synchronization due to stronger cortico-cortical synapses would also explain why the increase in power after wakefulness extends to other frequency bands besides the slow wave or delta band, although it remains to be explained why the time course of the increase varies for different frequency bands.

Slow wave homeostasis and synaptic downscaling
We have assumed that LTP-related changes occurring in the cortex during wakefulness lead to a net increase in synaptic weight onto neurons, and that such increase is reflected in increased amplitude of sleep slow waves. According to the hypothesis, such slow waves are not a mere epiphenomenon, but have a function to perform: to promote a generalized depression or downscaling of synaptic strength. Downscaling refers to a proportional reduction in the strength of all synapses converging onto the same neuron: if all synapses shed the same proportion of their weight, total synaptic weight can be reduced while preserving relative differences in synaptic strength and thereby memory traces.

Down- as well as up-scaling of cortical and hippocampal synapses have been observed both in vitro and in vivo. In these experiments, a proportional reduction of the strength of all synapses impinging on a neuron could be produced by artificially elevating synaptic input to that neuron for several hours, whereas a prolonged block of neural activity produced the opposite effect. Such activity-dependent mechanisms of synaptic scaling ensure that neurons maintain a regulated firing level in the face of uncontrollable changes in their inputs.

According to the hypothesis, sleep-dependent synaptic scaling would ensure primarily the homeostatic control of synaptic weight, and only indirectly of neuronal firing levels. Also, since wakefulness is assumed to result in net synaptic potentiation, sleep would serve primarily to scale
synapses down, rather than up. Like activity-dependent synaptic scaling, however, sleep-dependent downscaling would affect most or all of a neuron’s synapses. In this respect, downscaling is conceptually different from long-term depression, which affects select groups of synapses, or depotentiation, which affects only recently potentiated ones. Nevertheless, downscaling is likely to use many of the same molecular mechanisms involved in depression/depotentiation. Substantial evidence indicates that these forms of plasticity depend on the dephosphorylation and subsequent internalization of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors that ultimately leads to a reduction in synaptic efficacy.\(^{55,56}\) Whichsoever the specific mechanism, the hypothesis is that a generalized synaptic downscaling during sleep, including possibly the downselection or pruning of certain synapses, serves to ensure the maintenance of balanced synaptic input to cortical neurons.

**Evidence**

We have seen above that the amplitude and synchronization of sleep oscillations appear to reflect the strength of cortico-cortical connections. To the extent that this is true, the well-established exponential decrease of EEG SWA during sleep\(^2\) represents strong electrophysiological evidence for downscaling during sleep. Especially relevant is the finding that, if SWA is suppressed through acoustic stimuli during the first part of sleep, SWA increases greatly in the second part of sleep.\(^{57}\) Since slow waves must occur for sleep SWA to decline, they must be more than a mere epiphenomenon of sleep. A decrease in SWA as soon as we enter sleep has also been observed after learning tasks that increase SWA locally.\(^{24}\) Further evidence comes from multi-unit recordings where neurons that are coactivated during waking display correlated firing during sleep, presumably reflecting stronger synaptic links between them. Interestingly, the strength of the correlation, and presumably the strength of underlying synapses, decays rapidly (within 30 min) during the sleep episode,\(^{58}\) in line with downscaling (see also\(^{59}\)). Neuroimaging data showing a decrease in absolute levels of brain metabolism after sleep are also consistent with the hypothesis that synaptic strength is downscaled during sleep,\(^{11}\) (see below).

A role for sleep in downscaling is compatible with recent molecular evidence. We have seen that during sleep the expression of LTP-related molecules reaches a low level.\(^5\) On the other hand, sleep is associated with the upregulation of molecules implicated in depotentiation/depression.\(^6\) Such molecules include calcineurin, a phosphatase that dephosphorylates AMPA receptors strengthened during long-term potentiation, protein phosphatase 1, metabotropic glutamate receptor subunit 2, which is required for synaptic depression, and several proteins involved in vesicle recycling, such as N-ethylmaleimide-sensitive factor (NSF). Also, NREM sleep is associated with higher levels of insulin,\(^{60}\) which promotes the internalization of AMPA receptors and LTD.\(^{61}\) Thus, at least at the molecular level, sleep may not just be unfavorable to synaptic potentiation, but specifically conducive to synaptic downscaling. More direct tests of this prediction can be envisaged. It is already known that sleep altogether favors dephosphorylation in the brain.\(^{62}\) It now appears that sleep is associated with the selective dephosphorylation of AMPA channel residues involved in synaptic depression (Cirelli et al., in preparation).

Possible anatomical evidence for downscaling during sleep comes from studies showing that increases in synaptic density triggered by learning are evident for just a few hours, after which synaptic density returns to baseline. For example, rats who had learned the position of a hidden platform showed an increase in hippocampal synaptic density after 9 h of training (three training blocks at 3 h intervals). If left alone for 12 h followed by one last training block, rats remembered the location of the platform even better. However, synaptic density was down to control levels, as if the intervening 12 h with ad libitum sleep had reestablished synaptic homeostasis.\(^{63}\) It is not yet known, however, whether the return of synaptic density to baseline levels necessarily requires sleep as opposed to merely the passage of time.

Finally, functional evidence that NREM sleep may be associated with synaptic downscaling or with synaptic downselection 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 depression of cortical connections related to the deprived eye.\(^{40}\) 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 six more hours. Remarkably, an equivalent increase in depression can be seen if the animal is allowed to sleep for 6 h in the dark.\(^{64}\) This result has been interpreted in terms of sleep-mediated ‘consolidation’, but it could be due as well to sleep-dependent downscaling.
Mechanisms

Why would SWA lead to synaptic downscaling? As we have seen, the fundamental cellular phenomenon underlying NREM sleep rhythms is the slow oscillation, which is seen in virtually every cortical cell recorded intracellularly. Remarkably, the slow oscillation occurs at a frequency—less than 1 Hz—that is ideally suited to induce depotentiation/depression in stimulation paradigms. Low frequency oscillations during sleep may promote depression through changes in calcium dynamics, which are crucial for depression. The unique neuromodulatory milieu of NREM sleep—low acetylcholine, noradrenaline, serotonin, and histamine—may also be important, as well as the fact that BDNF, which prevents depression, is low in sleep. 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. 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. Alternatively, depolarization-hyperpolarization sequences might be sufficient to trigger downscaling. Yet another possibility is that depression may be powerfully triggered by the temporal pairing between generalized hyperpolarization at the end of the down-phase and generalized spiking at the beginning of the up-phase.

Whatever the precise mechanisms of SWA-dependent downscaling, an appealing feature of this entire process is that it could be self-limiting. As shown by computer simulations, the progressive reduction of synaptic strength due to SWA-dependent downscaling reduces 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 are less activated. Eventually, cortical cells stop alternating between crisp up- and down-phases, and hover instead around an intermediate membrane potential that prevents further downscaling. When this endpoint is reached, SWA has decreased exponentially to a minimum, and synaptic weight has returned to baseline. This notion is consistent with experimental studies showing that after 4-5 NREM sleep episodes SWA reaches an asymptote and remains at a fairly constant level.

The functional advantages of synaptic downscaling during sleep

According to the hypothesis, synaptic downscaling during sleep would offer several benefits. The most important benefits have to do with basic commodities in the brain, such as energy and space, but downscaling may also benefit learning and memory.

Energy savings

About 40% of the energy requirements of the cerebral cortex—by far the most metabolically expensive tissue in the body—are due to neuronal repolarization following postsynaptic potentials. The higher the synaptic weight impinging on a neuron, the higher this portion of the energy budget. Moreover, increased synaptic weight is thought to lead to increased average firing rates, and spikes in turn are responsible for another 40% of the gray matter energy budget. Therefore, it would seem energetically prohibitive for the brain to let synaptic weight grow without checks as a result of waking plasticity. Indeed, if PET data offer any indication, after just one waking day energy expenditure may grow by as much as 18%. Sleep, and the accompanying downscaling of synapses, would then be needed to interrupt the growth of synaptic strength associated with waking and prevent synaptic overload. The recalibration of cortical circuits during sleep would yield a brain that remains energetically efficient despite keeping trace of previous waking experiences.

Space savings

Another benefit of synaptic downscaling/downscaling during sleep would be in terms of space requirements. Synaptic strengthening is thought to be accompanied by morphological changes, including increased size of terminal boutons and spines, and synapses may even grow in number (e.g.). But space is a precious commodity in the brain, and even minuscule increases in volume are extremely dangerous. For example, neocortical gray matter is tightly packed, with wiring (axons and dendrites) taking up ~60% of the space, synaptic contacts (boutons and spines) ~20%, and the rest (cell bodies, vessels, extracellular space) the remaining 20%. Thus, sleep would be important not just to keep in check the metabolic cost of strengthened synapses, but also to curb their demands on brain real estate.
Benefits for learning and memory

Sleep-dependent downscaling may have additional benefits for learning and memory. For instance, it is likely that, due to the combined energy and space costs of uninterrupted synaptic plasticity, the ability of the brain to acquire new information would rapidly grind to a halt in the absence of downscaling. In this sense, sleep would not only be the price we have to pay for plasticity the previous day, but also an investment to allow the organism to learn afresh the next day. Indeed, in certain brain areas, such as the hippocampus, radical synaptic downscaling may be necessary to clean the slate and rapidly adapt to a new environment. Another benefit of downscaling/downselection would be to promote synaptic competition, which may be especially important during development, a time of exuberant synaptic growth. For example, connections between strongly correlated neurons would survive, while others may be eliminated.70

In the adult, downscaling could benefit learning in yet another way by increasing signal-to-noise ratios in the relevant brain circuits. To illustrate, consider again the visuomotor task discussed in connection with local slow wave homeostasis.24 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,71 and only after further practice does it converge upon more restricted foci of cortical activation.25 This pattern is not surprising, since visuomotor learning is an incremental process, during which early executions are inaccurate, and only slowly converge upon correct trajectories. Thus, it is likely that early on some synapses contributing to erroneous or imperfect movements may be potentiated (noise), although later on synapses contributing to a correct movement will become progressively more efficacious (signal). In Fig. 2, this is indicated by the appearance, in addition to the appropriately strengthened red synapse with a weight of 150, of a small red synapse with a weight of five.

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, silent, or disappear, synapses contributing to the noise, being on average much weaker than those contributing to the signal, would cease to interfere in the execution, and the signal-to-noise ratios would increase (in Fig. 2, this is indicated by the disappearance during sleep of the red synapse with a weight of five). Indeed, just as predicted, when subjects were tested after sleep following the rotation adaptation task, they showed a significant enhancement of their performance, which was absent in subjects who trained in the morning and were retested after 8 h of wakefulness. Moreover, performance enhancement after sleep was strongly correlated with the increase in SWA in the right parietal areas involved in the task. Finally, the strongest correlation (r = 0.9) was with the increase of signal-to-noise ratios during learning.

Other groups have found that sleep can indeed enhance performance in certain tasks.72–79 These studies generally assume that sleep may enhance performance by ‘replaying’ patterns of neural activity obtained during training in wakefulness. It is frequently suggested that such replay may actually potentiate synapses (e.g.80). The synaptic homeostasis hypothesis, by contrast, predicts that sleep may enhance performance by global downscaling, thanks to the postulated increase in signal-to-noise ratios. This possibility is more economical (and energy efficient), and has the important advantage of not requiring great fidelity in sleep ‘replays’ (see below). Nevertheless, downscaling and the relative potentiation of recently tagged synapses are not mutually exclusive, especially because downscaling should promote competition.

Is sleep necessary for synaptic homeostasis?

Any proposal about the function of sleep should be able to provide a convincing explanation of why the proposed function can only be fulfilled by sleep and not by quiet wakefulness.13 Otherwise, why would sleep—a potentially dangerous behavior characterized by loss of contact with the environment—be so universal, and why would sleep pressure be so overwhelming? While downscaling during wakefulness cannot be ruled out a priori, there are several reasons why sleep might be necessary. Perhaps the most important reason is that, in order to determine how much downscaling is needed to maintain synaptic homeostasis, a neuron should be able to assess its total synaptic input in an unbiased manner, which is to say off-line, independent of behavioral requirements. This is difficult to do during wakefulness. Suppose, the waking day is spent in reiterating certain behavioral tasks, so that certain neural circuits are strongly and repeatedly activated. Based on high average synaptic input, neurons partaking in such circuits would engage in a much heavier dose of downscaling that they actually need. During sleep, by contrast, neural activity occurs spontaneously and off-line, virtually disconnected from behavioral requirements. This
spontaneous activity is likely to reflect synaptic strength rather than outside influences. In this way, a neuron's synaptic input would represent an unbiased estimate of the synaptic strength impinging on it, and the neuron could downscale appropriately. Another reason why downscaling might best occur during sleep is that, at the molecular level, generalized changes in synaptic strength may be incompatible with the need to selectively increase the strength of certain synapses, as is the case during learning. And of course, to the extent that downscaling is promoted by repetitive depolarization—hyperpolarization sequences, these are perfectly compatible with sleep but would seriously interfere with behavior if they were to occur during wakefulness.

Some implications of the synaptic homeostasis hypothesis

To the extent that the main claims of the synaptic homeostasis hypothesis are justified by the available evidence, they offer a fresh perspective on several aspects of sleep and sleep medicine. In what follows, we will consider some intriguing implications of the hypothesis for neuroimaging studies, and briefly discuss the possibility that a dysregulation of synaptic homeostasis may be implicated in disorders such as insomnia and depression.

The synaptic homeostasis hypothesis, neuroimaging, and reactivation

Some of the most intriguing corollaries of the synaptic homeostasis hypothesis concern neuroimaging. As was mentioned above, it has been calculated that nearly 80% of cortical grey matter metabolism is related to neural activity. If half of it to support action potentials and half to support postsynaptic potentials. Thus, synaptic strength may control ~40% of the cortex energy needs directly, and potentially more because of indirect effects on firing rates. If, as predicted by the hypothesis, synaptic weight increases in the course of normal wakefulness, brain metabolism should also increase. Support for this prediction comes from PET experiments in humans and deoxyglucose studies in mice. The human study found a remarkable difference in the absolute value of cerebral blood flow at rest between an awake scan in the evening, after a variable schedule of partial sleep deprivation, and an awake scan in the morning, after several hours of sleep. Blood flow was measured with O15, and its value, corrected for arterial pCO2, relates to cerebral oxygen utilization and therefore to metabolic rate. Quite unexpectedly, absolute blood flow values were 18% higher at the end of the waking day than after a night of sleep, and this was the case almost everywhere in the brain. A change of this magnitude is not usually seen in PET studies, even less so when comparing two identical ‘resting’ conditions, but it would be consistent with a net increase in synaptic strength during wakefulness. The deoxyglucose study in rats is also consistent with this picture, in that glucose utilization was considerably higher in waking before sleep than in waking after sleep. Also consistent is a study using transcranial Doppler ultrasonography, where waking cerebral blood flow velocity in the middle cerebral artery was 6.6% lower post-sleep compared to pre-sleep. Another study showed that cerebral blood flow velocities are significantly higher during the first NREM sleep episode than during the second or the last. Even for the same sleep stage, such as stage 2, values were always lower later in the night. Indeed, the average decrease of blood flow velocity during a night of sleep parallels closely the decrease of SWA. Further studies comparing absolute values of brain glucose and oxygen consumption (and other metabolic parameters) before and after sleep in a standardized waking condition, should help establish whether normal wakefulness is indeed accompanied by a generalized increase in brain energy requirements. Equally important, they should determine to what extent changes in blood flow and metabolism between evening and morning are due to sleep rather than, for example, to a circadian modulation of arousal.

The hypothesis also predicts that intense learning tasks triggering local synaptic changes in specific brain regions may lead to a local hypermetabolic ‘trace’ under resting conditions (or during the performance of unrelated tasks). This is because, to the extent that learning the task leads to an increase in synaptic strength in specific brain regions, those regions should show an increase in metabolic need even at rest, when they are undergoing spontaneous activity. On the other hand, such hypermetabolic traces should be progressively normalized over a sufficiently long period of sleep. According to the hypothesis, several imaging experiments showing a ‘reactivation’ during stages of sleep (both NREM and REM) after learning a task, could then be interpreted as showing a metabolic trace of the induction of synaptic potentiation during previous wakefulness. The hypothesis predicts that such traces should be visible also in subsequent wakefulness, but should decrease in intensity in the course of sleep. By the
same token, the hypothesis suggests that the
electrophysiological instances of 'replay'\textsuperscript{58,89-93}
can also be interpreted as a 'trace' of synaptic
strengthening induced during previous wakefulness,
expressed in this case as correlated spontaneous
firing. Consistent with this idea, electrophysiologi-
cal experiments indicate that the so-called replay
also occurs during quiet wakefulness,\textsuperscript{58} and that its
intensity decreases in the course of sleep, at least
in the hippocampus. Multielectrode recordings in
multiple forebrain structures also indicate that,
while multiunit activity patterns observed in a sleep
episode do bear a statistical relationship with the
activity patterns triggered by previous waking
experiences, the similarity is extremely low-fide-
licity.\textsuperscript{93} If neural activity during sleep resulted in
synaptic potentiation, as is sometimes claimed,
what would be learned during sleep would be
mostly noise, rather than signal.

**Dysregulations of synaptic homeostasis and
cognitive impairment**

From the clinical perspective, one of the most
relevant predictions of the synaptic homeostasis
hypothesis is that, if the process of synaptic
homeostasis is prevented by sleep deprivation or
sleep restriction, symptoms related to synaptic
overload of neocortical and limbic circuits should
follow. These could include cognitive impairment,
loss of sleep-related performance enhancement,
emotional impairment, difficulty concentrating,
and fatigue. Such symptoms are expected to occur
because synaptic overload should cause metabolic
overload, neuropil crowding, a decrease in neuronal
signal-to-noise ratios, and a reduction of the
capacity for plastic change. Metabolic overload, in
turn, may lead to compensatory reactions, such as
a homeostatic reduction in neuronal excitability or
increased synaptic failure. Thus, two kinds of
symptoms should be expected after sleep depre-
vation and sleep restriction: (i) 'sleepiness'
(increased propensity to fall asleep) and related
symptoms, due to globally increased sleep pressure
and mediated by central homeostatic mechanisms;
and (ii) 'non-restorative symptoms' (cognitive
impairment, fatigue etc.) due to the local effects
of sleep loss on cortical and limbic circuits, and
mediated by synaptic overload or homeostatic
changes in excitability. The hypothesis also
suggests that a dysregulation of synaptic homeo-
stasis may be implicated in certain neuropsychiatric
disorders. Specifically, symptoms resulting from
dysregulation of synaptic homeostasis are likely to
be prominent in sleep disorders such as primary
insomnia and syndromes characterized by the
subjective feeling of non-restorative sleep, as
well as in psychiatric disorders characterized by
significant sleep disturbances, such as depression.

Primary insomnia is a 24-h disorder in which
subjective feeling of non-restorative sleep is
associated with fatigue, difficulty concentrating,
cognitive impairment, irritability and mood
changes,\textsuperscript{94-96} all features that may result from
impaired synaptic homeostasis. Primary insomnia
is often associated with hyper arousal,\textsuperscript{97,98} which is
likely to impair synaptic homeostasis during sleep.
Recent neuroimaging studies have shown that
insomniacs have globally increased brain metab-
olism during both waking and sleep, possibly a
reflection of hyper arousal, but show relative
reductions of glucose metabolism in prefrontal
cortex, possibly due to insufficient sleep restor-
ation. Indeed, during sleep insomniac patients fail
to deactivate medial prefrontal cortex, anterior
cingulate cortex, and parts of the thalamus,
suggesting a disruption of homeostatic mechan-
isms.\textsuperscript{98} In line with this suggestion, recent studies
suggest that enhancing sleep homeostasis using
sleep restriction can result in the improvement of
insomnia.\textsuperscript{99} According to the hypothesis, then,
some of the symptoms of primary insomnia may
be due, at least in part, to synaptic overload and to
compensatory changes in neuronal excitability.

Major depression shares many of the same
symptoms with primary insomnia. Sleep disturbances
such as insomnia or hypersomnia are defining features
of the disorder. Major depression and insomnia are
epidemiologically related, and individuals with
insomnia are more likely to develop depression than
normal sleepers.\textsuperscript{100} Abnormalities of sleep structure,
such as disruption of slow wave sleep and increased
REM sleep latency, are common features of
depression, as are changes in SWA during baseline
sleep. Imaging studies have pointed to local
brain abnormalities, such as hypofrontality during
both wakefulness and sleep, and smaller sleep-
related decrements in activity in fronto-parietal
areas. Moreover, several studies indicate that
sleep deprivation, which provides an acute challenge
to sleep homeostasis, can ameliorate many of the
symptoms of depression.\textsuperscript{104} Also, acute sleep depre-
vation and chronic antidepressant treatment result in
the induction of a similar set of genes involved in
synaptic potentiation, such as \textit{BDNF} and \textit{P-CREB}.\textsuperscript{105}

The synaptic homeostasis hypothesis suggests
that, at least in some cases, a local reduction of
slow wave homeostasis may reflect an insufficient
level of synaptic strength during wakefulness. For
example, in a proportion of depressed subjects, in
line with neuroimaging reports of reduced
prefrontal activation (hypofrontality), baseline synaptic strength in certain cortico-limbic circuits may be lower than normal. As predicted by the hypothesis, this local reduction of synaptic strength should be evident as a local reduction of SWA during sleep. According to the hypothesis, then, these subjects would be expected to improve with sleep deprivation because extended wakefulness would potentiate those very circuits to reach normal levels of synaptic strength. In fact, depressed subjects who respond best to sleep deprivation are those who report a diurnal improvement in mood. On the other hand, the occurrence of synaptic downscaling during sleep would explain why the antidepressant effects of sleep deprivation are typically short-lasting. The hypothesis also suggests that, in such patients, therapeutic approaches aimed at locally potentiating synaptic strength, such as targeted transcranial magnetic stimulation, or specific learning tasks, ideally augmented by noradrenergic agonists, would be most effective if systematically applied every morning.

At the present stage, these suggestions are necessarily tentative and imprecise. Nevertheless, the notion that disturbances in sleep-related synaptic homeostasis may play a significant role in the pathogenesis of psychiatric and neurological disorders is worth considering whenever there is evidence for an imbalance of plastic or metabolic neuronal processes.

### Conclusion

In summary, the synaptic homeostasis hypothesis makes four main claims: (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 neural function and, indirectly, on performance. From these claims derive several intriguing possibilities, including the possibility that a dysregulation of synaptic homeostasis may be implicated in disorders such as insomnia and depression. Moreover, the hypothesis has relevant implications for neuroimaging studies.

The hypothesis also triggers some further questions that have not been addressed here. For example, what are the complex relationships between the local regulation of sleep as mediated by synaptic homeostasis, and the global regulation of sleep as mediated by hypothalamic and brainstem centers? How does the hypothesis apply to brain structures other than the cerebral cortex where sleep rhythms are different, such as the hippocampus? Or to other species, such as the fruit fly? Can the changes in SWA homeostasis also be affected by changes in the balance between excitatory and inhibitory circuits? Moreover, what is the role of REM sleep? And what is the role of sleep spindles, given that their time course and homeostatic regulation differ from those of SWA?107,108 Another issue concerns the effects of sleep deprivation and sleep restriction. Specifically, what happens if synaptic downscaling is prevented from occurring or is incomplete? Do other mechanisms intervene to reduce neuronal excitability and thereby metabolic needs?109 This question is particularly important since during chronic sleep restriction SWA reaches a steady state, whereas performance deficits are cumulative.110 Finally, what are the implications of the hypothesis concerning pharmacological treatments? Do drugs that reduce SWA, such as benzodiazepines, negatively affect downscaling and thereby sleep restoration? Conversely, can synaptic downscaling be potentiated by pharmacological agents that can exaggerate the slow oscillations of NREM sleep?

Altogether, the main claims of the synaptic homeostatic hypothesis are consistent with a large body of evidence at the behavioral, molecular, and neurophysiological level, and with results obtained with techniques ranging from computer simulations

### Research agenda

To validate the synaptic homeostasis hypothesis, we need to test some of its key predictions:

- waking behaviors associated with synaptic potentiation should be followed by an increased SWA homeostatic response during sleep. This can be tested for example using learning tasks, enriched environment, or high-frequency electrophysiological stimulation
- waking behaviors associated with synaptic depression should be followed by a blunted SWA homeostatic response during sleep. This can be tested for example by using sensory deprivation paradigms or low-frequency electrophysiological stimulation
- brain metabolism should increase during wakefulness and decrease after sleep. This can be tested using deoxyglucose studies in animals and various neuroimaging approaches in humans
- learning a task should leave a metabolic trace in the involved area that is visible under resting conditions and is reduced after sleep.
to human neuroimaging. The very fact that the hypothesis accounts for such disparate results represents one of its more appealing features. However, it should be made clear that several aspects of the hypothesis are still speculative. Most of these aspects, fortunately, lend themselves to stringent experimental tests.

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* The most important references are denoted by an asterisk.


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