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Impacts of Sleep Loss versus Waking Experience on Brain Plasticity: Parallel or Orthogonal?

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Abstract

Recent studies on the effects of sleep deprivation on synaptic plasticity have yielded discrepant results. Sleep deprivation studies using novelty exposure as a means to keep animals awake suggests that sleep (compared with wake) leads to widespread reductions in net synaptic strength. By contrast, sleep deprivation studies using approaches avoiding novelty-induced arousal (i.e., gentle handling) suggest that sleep can promote synaptic growth and strengthening. How can these discrepant findings be reconciled? Here, we discuss how varying methodologies for the experimental disruption of sleep (with differential introduction of novel experiences) could fundamentally alter the experimental outcome with regard to synaptic plasticity. Thus, data from experiments aimed at assessing the relative impact of sleep versus wake on the brain may instead reflect the quality of the waking experience itself. The highlighted work suggests that brain plasticity resulting from novel experiences versus wake per se has unique and distinct features.

Resolving the Plasticity Functions of Sleep in the Brain

Sleep behavior is conserved across animal phyla, and sleep appears to be critical both for appropriate function in wake, and ultimately, for survival. Some features of sleep behavior, such as its prevalence during early life in many species, have suggested that the sleeping brain state promotes experience- dependent remodeling of the brain. A large body of research has shown that throughout the human lifespan, there are numerous cognitive benefits of sleep. What aspects of sleep mediate these effects on the nervous system? Work aimed at clarifying the physiological benefits of sleep, and why sleep loss is so detrimental, has profiled numerous effects of experimental sleep deprivation on the brain.

Studies examining the molecular and cellular impact of sleep deprivation have generally fallen into two categories: (i) those suggesting that sleep leads to synaptic downscaling throughout the brain (while spontaneous wake or experimental sleep deprivation promote net synaptic growth and strengthening); and (ii) those that indicate a role for sleep in the strengthening of synapses following learning (with experimental sleep deprivation having the opposite effect). In this opinion article, we aim to reconcile these seemingly

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contradictory findings. We first provide an overview of work suggesting these opposite effects of sleep deprivation on synaptic strength, focusing on implications for hippocampal and cortical plasticity. We then discuss issues of experimental methodology that could contribute to these divergent effects (Figure 1), as well as other methodological issues that may impact the consequences of sleep and sleep loss on the brain.

Evidence for Net Synaptic Strengthening in Wake and Net Weakening in Sleep

A prominent hypothesis regarding the function of sleep for the brain is the synaptic homeostasis hypothesis, which proposes that sleep leads to a beneficial net weakening of (excitatory) synapses in circuits throughout the brain [1]. The hypothesis is supported by data from studies of synaptic structures in the neocortex and hippocampus using experimental sleep deprivation. The hypothesis is supported by several lines of data. The first indicates that spontaneous wake or experimentally prolonged sleep loss in rats causes firing rates among barrel cortex neurons to gradually increase [2]. While this change could be due to changes in intrinsic excitability, excitatory/inhibitory balance, or neuromodulation alterations during sleep deprivation, in light of additional evidence (described below) these changes in firing have been attributed to increases in excitatory synaptic strength. Second, 4–6-h prolonged wake is associated with increased phosphorylation of AMPA receptors (AMPARs), CaMKII, and GSK3beta in both hippocampal and neocortical synaptoneurosomes of mice and rats (all indicative of glutamatergic synapse potentiation) [3,4]. Using serial electron microscopy (EM), it was shown that 6–7 h of enforced wake leads to an increase in the axon–spine interface and spine head volume in mouse somatosensory and motor cortices [5]. Analyses of the hippocampus using a partially overlapping cohort of mice indicated that enforced wake lead to a redistribution to larger sizes of the axon–spine interface in perforated synapses only. There was no associated change in non-perforated synapses (although the authors reported a nonsignificant trend of increase) or perforated synapse density [6]. Similarly, *in vivo* imaging in mice indicated that 6–7 h of experimental sleep deprivation, or spontaneous wake at night, leads to relative increases in the rate of spines formed and decreases in the rate of spines lost in barrel cortex dendrites, relative to uninterrupted daytime sleep [7]. Together, these data have built a case for net synaptic strengthening across wake and, conversely, net synaptic weakening across periods of sleep.

Evidence for Net Synaptic Strengthening during Sleep and Net Weakening during Wake

Work examining plasticity in both the neocortex and the hippocampus have found evidence that experimental sleep deprivation disrupts, rather than promotes, synaptic potentiation. For example, increases in primary visual cortex (V1) neurons' firing rate responses to visual stimuli are seen after a period of sleep in both mouse [8–10] and cat [11,12] following novel visual experiences. As discussed above, while firing rate changes alone could be due to many cellular or network processes, these effects are stimulus specific and linked to a Hebbian plasticity mechanism (NMDA receptor-dependent long-term potentiation [LTP];

[13,14]). In both systems, this sleep-associated response potentiation is associated with biochemical hallmarks of synaptic potentiation and are dependent on pathways mediating LTP [11,15,16]. Both forms of plasticity and associated molecular events are disrupted by experimental sleep deprivation. Similarly, evoked responses are potentiated in an AMPAR- and NMDA receptor-dependent manner in the cat somatosensory cortex over a period of slow-wave sleep [17]. In line with these observations in the cortex, 5–6-h sleep deprivation attenuates long-lasting forms of hippocampal LTP in mice that require the cAMP, LIMK–cofilin, and mTOR pathways [18–21]. Brief experimental sleep loss has also been shown to disrupt Arc expression [22] and AMPAR phosphorylation [23] in the mouse hippocampus.

There are also data suggesting that synaptic structures can be preferentially enhanced during sleep or disrupted by sleep loss. Sophisticated *in vivo* imaging studies have shown that following training on a motor task, new dendritic spines are formed and stabilized in motor cortex neurons in freely sleeping mice but not in those that are deprived of sleep [24,25]. In the dorsal adult mouse hippocampus, 5–6-h sleep deprivation leads to a reduction in dendritic spine numbers in CA1 pyramidal neurons (e.g., [18,20]) and dentate gyrus (DG) granule cells [26] (for a review, see [27]). Together, these electrophysiological, biochemical, and neuroanatomical studies support conclusions contradicting the synaptic homeostasis hypothesis – namely, that synaptic potentiation can occur across sleep and synaptic growth and strengthening can be disrupted by sleep deprivation.

How do neuroscientists reconcile the seemingly contradictory findings linking sleep to either synaptic weakening or synaptic strengthening? Does sleep loss itself lead to synaptic strengthening, weakening, or perhaps both? In the next section, we discuss how subtle differences in methodological approaches and experimental design may drastically influence the outcome of studies linking sleep and sleep loss to synaptic structure and function.

Effects of Brain State versus Experience on Synaptic Plasticity

Experimental methodology to enforce wake varies extensively between laboratories. To keep rodents awake for a short duration of time (i.e., a few hours), many laboratories have adopted ‘gentle handling’ procedures; however, the precise method of handling involved can vary. Some laboratories appear to aim at providing the minimal sensory stimulation necessary to promote wake, but simultaneously avoiding highly novel experience or forcing high levels of loco-motor activity. Procedures for this form of gentle handling involve multiday habituation prior to sleep deprivation. Mice are housed in the same home cage and room that the deprivation will occur in and are handled daily by the experimenters [28]. The sleep deprivation method itself (also referred to as ‘mild stimulation’) includes keeping animals in their home cage and interrupting transitions to sleep by tapping on the cage wall, gently moving the cage itself, or, if necessary, disturbing the nesting material in the cage. Other interventions include using brushes or cotton tipped applicators to stroke or gently tap animals to prevent sleep transitions. This method of sleep deprivation has been validated in mice using EEG measurements and prevents all rapid eye movement (REM) sleep and approximately 95% of non-REM (NREM) sleep [8,29,30]. A major goal of this method is to keep animals awake over a period of hours without exposing them to novel or highly arousing stimuli.

For people in real-world conditions, sleep loss is often self-imposed and associated with novel experiences, social interactions, and high levels of activity. For this reason, and because novel experiences can be highly effective (from an experimental standpoint) at promoting wake in animals, some laboratories have turned towards using exposure to novelty as a strategy for sleep deprivation. This includes placing animals in novel cages, exposing animals to novel objects or bedding from other cages, providing novel treats, and/or giving first-time access to a running wheel during the light (rest) phase of the circadian cycle. As a strategy for keeping animals awake, this method is highly effective, as animals tend to be highly aroused and active in the context of novel experiences.

Critically, all of the studies described previously in the section ‘Evidence for Net Synaptic Strengthening in Wake and Net Weakening in Sleep’ have used novel sensory stimuli to enforce wake (Table 1); by contrast, much of the work highlighted in the section ‘Evidence for Net Synaptic Strengthening during Sleep and Net Weakening during Wake’ has used either gentle handling methods of sleep deprivation or techniques that minimize direct sensory input to the circuit under study (e.g., conducting sleep deprivation in darkness to study plastic changes to V1) (Table 2). We propose that these differences in methodology are a major cause for discrepancies between the two sets of studies with regard to changes in plasticity-related gene expression, physiology, and anatomy across periods of extended wake (Figure 1).

This discrepancy based on method raises the question: which method is optimal? One serious caveat of using novelty to enforce wake in studies relating to brain function is that novelty drives synaptic plasticity throughout the brain. Thus, in these experiments it is nearly impossible to discriminate between the impact of prolonged wake and the impact of novel experiences on synaptic plasticity. For example, exposure to novel objects alone increases the amplitude of evoked potential responses to perforant path input (an indicator of synaptic potentiation in the DG and elsewhere [13,31,32]), increases Fos protein expression in the rodent hippocampal DG (e.g., [33,34]), and elevates Fos expression in the occipital cortex, perirhinal cortex, and anterior cingulate gyrus [35]. Environmental novelty (e.g., simple placement in a novel arena) increases neuronal activity (i.e., Fos protein expression) throughout the rat hippocampus [36,37].

Another example of novel experience being an experimental confound is illustrated by a series of experiments showing dendritic spine morphological changes (i.e., increases in the size of axon–spine interfaces) following a few hours of enforced wake. Measures were made using serial EM to quantify dendritic structures in the primary somatosensory (S1) and primary motor (M1) cortex following ad lib sleep versus following wake enforced in mice through exploration of novel objects and use of a running wheel [5]. As mentioned, novel objects and running wheels produce widespread plasticity throughout the brain, but physical interaction over a prolonged interval of time with objects (and particularly with a running wheel) has long been known to selectively induce plasticity in S1 and M1 [38–42]. In a more striking example, dendrites were measured in M1 of mouse pups, following ad lib ‘sleep’ (defined as immobility) versus enforced ‘wake’ (defined as locomotion) [43]. There is general agreement that motor activity can drive M1 plasticity, as evinced, for instance, by the use of locomotion (or other forms of motor practice) in rehabilitation for stroke or other

brain injuries affecting motor function in humans [44–48]. The effects of forced locomotion on motor cortex plasticity has been extensively studied in rodents, with clear increases in the expression of plasticity-related genes, functional plasticity, and anatomical remodeling [49–52]. So, could the effects of enforced waking on M1 dendritic spines be entirely due to forced locomotion rather than brain state? This seems likely in view of other published observations. For example, extended wake across a day reversed (rather than enhanced) the effects of motor training in humans in augmenting motor cortex excitability [53]. In mice, sleep deprivation by gentle handling reverses, rather than enhances, the effects of single-trial motor learning on M1 dendritic spine formation [24]. Furthermore, as shown in Table 2, sleep deprivation using similar techniques (objects, play, locomotion) seems to have the opposite effect in cat V1 neurons during the critical period, provided visual input is prevented during this time [11,15]. These findings suggest that enforced motor activity, rather than enforced wake, gives rise to the plastic changes reported in cortical neurons in these regions.

Together, these examples underline the idea that the experimental methodology for promoting wake is varied, and these methods have widespread implications for synaptic plasticity. While the precise behavioral and physiological mechanisms (e.g., stress/arousal, hormonal changes, Hebbian mechanisms) by which exposure to novel stimuli drives plasticity may be diverse, the fact remains that increased exposure to these stimuli drives plasticity. Thus, for any studies attributing function regarding plasticity mechanisms to sleep versus wake brain states, it is vital to minimize plasticity caused by the sleep deprivation method – an effect orthogonal to (and possibly opposite to) the effects of sleep loss itself. In our view, novel environments, experiences, and objects should be avoided in experiments aiming to identify synaptic events occurring as a function of sleep versus wake.

Additional Caveats: Effects of Age, Sex, and Circadian Phase on Synaptic Structure and Plasticity

Additional methodological considerations are essential to fully clarify how sleep and wake affect synaptic function. For example, several studies (e.g., [4]) have used the collection of brain samples at circadian timepoints (e.g., a few hours into the light versus dark phase) as a proxy for sleep and wake. Depending on the species, this strategy may be essential for studies not relying on experimental sleep deprivation. For example, rats and mice (and other species such as cats) have very few periods of spontaneous sustained wake (lasting tens of minutes or longer) during the light phase in their standard home-cage environment [54]. While relative sleep amounts do vary (to an extent that varies by species) across the light–dark cycle, recent work in mice has demonstrated that the synaptic abundance of both mRNAs and proteins associated with synaptic plasticity is regulated primarily as a function of time of day (rather than as a function of sleep versus wake) [55]. Therefore, synaptic differences between samples taken at different circadian timepoints are likely to be due to clock-mediated factors, not sleep and wake amounts.

A second methodological issue is animal sex as a biological variable. Many studies have used a combination of male and female mice (sometimes in unknown ratios) in various

treatment groups. This almost certainly is a confounding variable with regard to synaptic structure. In part, the estrus cycle is accompanied by about 30% change in dendritic spine numbers in structures like the hippocampus and neocortex, mediated by changes in estradiol [56–59], as well as cyclic changes in sensory evoked plasticity [60]. Further, sleep architecture, sleeping EEG activity, and apparent sleep need all seem to vary as a function of the estrous cycle [61]. Besides the estrus cycle, there are likely to be additional sex differences that contribute to altered sleep and synaptic plasticity.

A final methodological issue of concern for studies of synaptic structure and function is the age of experimental animals used in these studies. Many studies aimed at assessing the role of sleep and wake in synaptic weakening versus strengthening (or elimination versus formation) have used what can be considered ‘adolescent’ animals (e.g., 3–4-week-old mice). Critically, across species (i.e., humans, monkeys, and mice) this stage of development is characterized by large-scale synaptic elimination and strengthening of inhibitory (relative to excitatory) connections [62–64]. Thus, comparisons of sleep and wake effects on spine formation, elimination, or density in studies using mice in the adolescent age range with experiments using more mature animals may yield discrepant findings.

Concluding Remarks

The general discordance of findings between studies using gentle handling and studies using novelty regarding the synaptic effects of sleep loss suggests that these differences are driven in a large part by methodology. It is perhaps unsurprising that enforced wake via novel experiences and locomotion leads to evident synaptic strengthening in brain regions such as the hippocampus, and particularly in S1 and M1 where many of these results have been reported. It is also arguably unsurprising that, by contrast, enforced wake with minimal sensorimotor experience results in less, or no, apparent synaptic strengthening. Together, these discrepancies underscore the notion that the sleep deprivation method per se has a substantial impact on brain plasticity, which can obscure effects due purely to individual animals’ sleep versus wake amounts. Concordant with these discrepancies, two largely opposing theories have emerged regarding the impact of sleep and wake states on brain plasticity. One theory (the synaptic homeostasis hypothesis [65]) proposes that sleep decreases synaptic strength throughout the brain while wake increases synaptic strength. Of note, studies supporting this theory are typically ones where experimental sleep deprivation is achieved using novelty methods. Further, animal age and sex, as well as circadian time, are confounding factors in some of these studies. The second theory proposes that sleep can augment synaptic strength following learning and that extended wake blocks these effects [66]. Studies supporting this idea have generally focused on brain regions engaged by prior learning and used gentle handling techniques aimed at minimizing sensory stimulation as a method for experimental sleep deprivation. However, a full description of gentle handling effects under different conditions (i.e., following learning versus no learning) is still lacking. For example, while the effects of gentle-handling sleep deprivation on neocortical synapses are well described following learning [66], less is known about the effects under steady-state conditions. This is in contrast to the hippocampus, where the effects of gentle handling on sleep loss outside learning are well described [27,67]. To further test these hypotheses, a full characterization of different sleep deprivation methods’ effects on synapses is essential. It

remains to be determined whether sleep and wake have consistent effects on synaptic strength throughout the brain. In addition, methodological caveats (e.g., age, sex differences, circadian time) must be taken into account.

The essential functions of sleep in regulating synapses can be further clarified by studying the effects of sleep and sleep deprivation across phylogeny. The studies described here were focused on the mammalian neocortex and hippocampus, where much of the seminal work on experience-dependent synaptic plasticity has been performed. Critically, however, alterations in synaptic structure have also been reported across period of sleeps or sleep deprivation in invertebrate species, including Drosophila [68,69] and Caenorhabditis elegans [70]. Addressing the question of how experience during wake interacts with sleep loss in these species (with simpler, more experimentally tractable nervous systems) may deepen our understanding of data from mammalian studies by providing an evolutionary context (see Outstanding Questions).

Finally, while comparisons between sleep and sleep deprivation may be enlightening, recent data suggest that different states and features of sleep (e.g., REM versus NREM sleep, specific sleep oscillations) have differential effects on synaptic plasticity. For example, two-photon imaging of dendrites in mice has shown that while spines are formed preferentially during post-learning NREM sleep [24], spines are pruned (and newly formed spines are selectively strengthened) during post-learning REM [25]. Future studies are needed to determine how specific sleep states and state-specific activity patterns [71] contribute to synaptic function. The use of opto- and pharmacogenetics to selectively manipulate, increase, decrease, or mimic sleep-associated activity patterns in specific brain circuits [10,30,72–75] may provide new insight into these questions. In the context of sleep deprivation studies, these techniques may even bypass the need for externally driven sleep deprivation as an essential experimental strategy and could therefore reveal causal roles for specific features of sleep states in regulating synaptic plasticity.

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Highlights

Sleep deprivation has been reported to either strengthen or weaken neocortical and hippocampal synapses, with results varying between studies using distinct methods used to keep animals awake.

Novelty exposure as a method to promote wake in experimental animals can lead to a net increase in synaptic strength in regions including the hippocampus, M1, and S1. These effects of environmental novelty can be difficult to disentangled from effects of prolonged wake per se.

Sleep deprivation using the gentle handling method is aimed at avoiding novelty-induced synaptic plasticity. Gentle-handling sleep deprivation (in contrast to novelty-induced sleep deprivation) can cause a net decrease in synaptic strength in both the hippocampus and the neocortex.

Fluctuations in gonadal hormones during the estrus cycle (and biological differences between males and females) can cause large-scale changes in neocortical and hippocampal spine density and synaptic efficacy. These changes can mask the effects of learning or sleep–wake cycles on synapses.

Circadian rhythms may modulate synaptic structure and function independent of sleep and wake. Thus, in studies comparing timepoints across the 24-h light–dark cycle, it is nearly impossible to dissociate the impact of circadian time from other factors such as sleep and wake on synaptic plasticity.

Outstanding Questions

To what extent is synaptic strength affected by the presentation of novel stimuli or tasks during sleep deprivation? Resolving this question will require a direct comparison of the effects of different methods of sleep deprivation (i.e., gentle handling versus provision of novel stimuli) on synapses in the hippocampus and cortex.

Because memory consolidation is initiated by experience in wake, there must be circuit-specific changes occurring during sleep that are set up by prior learning. What is the nature of circuit-specific changes in sleep (e.g., at the molecular and network activity level) and what are the experience-dependent mechanisms required to initiate them?

How widespread and uniform are effects of sleep and wake states on synapses? Are sleep-dependent changes in synaptic strength circuit or cell-type specific? For example, are excitatory and inhibitory synapses similarly affected by sleep and wake?

How do interactions between sleep/wake states and the estrous and circadian cycles regulate brain plasticity? Do these variables act on the same molecular substrates or do they each affect synaptic structure and function through independent signaling mechanisms?

What features of sleep states critically impact plasticity? Sleep and wake affect numerous aspects of brain physiology, including (but not limited to) effects on neuronal activity patterns, neuromodulation, transcription, and translation. Recently developed genetic tools may further our understanding of specific features of sleep states that are essential for brain plasticity and cognitive benefits.

Figure 1. Different Methodologies for Induction of Sleep Deprivation Result in Divergent Effects on Synaptic Strength.

In the past few years, studies have reported that prolonged wake either increases net spine numbers and synaptic strength or (conversely) decreases synaptic strength. These discrepant observations could be explained by examining the methodology used in these studies to enforce wake. We propose a hypothetical scenario in which the magnitude of novel sensory stimuli (associated with both sleep deprivation methods) and prolonged wake itself have opposite effects on net synaptic strength. These effects (relative to sleep) are shown in the graph at the left. Provision of novel sensory stimuli alone (broken red line) leads to maximal increases in net synaptic strength in the neocortex and hippocampus. This increase is partially mitigated by the effects of wake itself (broken blue line) during novel-stimulus-induced sleep deprivation (unbroken red line). This is because prolonged wake alone (broken blue line) tends to reduce synaptic strength. Gentle handling (mild sensory stimulation) leads to a more moderate increase in net synaptic strength in the neocortex and hippocampus (broken violet line), which is similarly mitigated by the effects of wake itself (broken blue line) during gentle-handling sleep deprivation (unbroken violet line).

Table 1.

Overview of Methodological Aspects and Outcomes of Experimental Studies Showing Net Synaptic Weakening in Sleep

Species	Sex	Age	Brain region studied	Sleep deprivation method	Result following sleep deprivation	Refs
Rat	Male and female	11–12 weeks	Barrel and frontal cortex	Novel objects Tapping on cage	Increased firing rate, which reversed during recovery sleep	[2]
Rat	Male and female	11–12 weeks	Whole neocortex	Novel objects	Increased phosphorylation and protein levels of AMPARs Elevated phosphorylation levels of CaMKII, GSK3beta	[3]
Mouse	Not defined	8–10 weeks	Hippocampus	Novel cage Tapping on cage Disturbing bedding	Increased phosphorylation and protein levels of AMPAR subunits driven by homer1a	[4]
Mouse	Male and female	~4 weeks	M1 and S1	Novel objects Running wheel Tapping on cage	Increased axon-spine interface and elevated spine head volume in weaker, more plastic spines	[5]
Mouse	Male and female	4 weeks	Hippocampus	Novel objects Tapping on cage	Increased axon-spine interface Increase in non-perforated spines	[6]
Mouse	Not defined	23–44 days	Barrel cortex	Novel objects Running wheel	Net increase in cortical spines	[7]
Mouse	Male and female	2 weeks	M1	Forced locomotion	Increased axon-spine interface	[43]

Table 2.

Overview of Methodological Aspects and Outcomes of Experimental Studies Showing Net Weakening during Wake

Species	Sex	Age	Brain region studied	Sleep deprivation method	Result following sleep deprivation	Refs
Mouse	Male	2–6 months	V1	Gentle handling (in darkness)	Disruption of orientation-selective potentiation of firing responses after visual experience	[8,9]
Cat	Male/ female	28–42 days	V1	Gentle handling, novel objects, play, forced locomotion (in darkness)	Reduced phosphorylation of GluR1, CaMK2a, and potentiation of visual responses	[11]
Cat	Male/ female	28–42 days	V1	As above	Reduced Arc expression	[15]
Mouse	Male	8–12 weeks	Hippocampus	Gentle handling	Impaired L-LTP Increased cofilin activity Spine loss in CA1 Recovery sleep reverses CA1 spine loss	[18]
Mouse	Male	8–12 weeks	Hippocampus	Gentle handling	Impaired protein synthesis Attenuated mTORC1-mediated phosphorylation of 4EBP2	[19]
Mouse	Male	8–12 weeks	Hippocampus	Gentle handling	Impaired long-lasting forms of LTP that depend on cAMP Decreased pCREB levels Increased PDE4A5 protein levels	[21]
Mouse	Male	12–14 weeks	Hippocampus	Gentle handling	Reduced Arc mRNA and protein expression in DG, no change in protein in CA1/3	[22]
Mouse	Male/ female	4 weeks	M1	Gentle handling	Reduced dendritic spine formation	[24]
Mouse	Male	8–12 weeks	Hippocampus	Gentle handling	Spine loss in DG	[26]