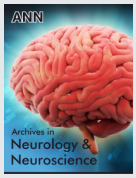

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Mini Review Article

Sleep-Dependent Sensory Gating and Synaptic Priming Mechanisms

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Abstract

The synaptic homeostasis hypothesis (SHY), a leading hypothesis on sleep, proposes that sensorial input during wakefulness increases synaptic potentiation, diminishing available neuroplastic capacity for future learning and so requiring renormalization during sleep. Faced with ongoing novelty, the organizational resources of brain synapses are posited to regularly operate within physical ranges that encounter upper limits. Sleep, accordingly, is considered vital not merely for the restoration of depleted resources but for preservation of the ability to optimally utilize sensorial information and neuroplastic resources. Based on this understanding, several structural and functional outcomes can be predicted, which have been supported by empirical observation. First, the acquisition of neuroplastic change is confined to periods of waking, when responsivity is maximal, rather than during sleep, when neural activity is at least partly disconnected from the external world. Second, such change occurs globally; that is, at a minimum it is found in all brain domains having sensorial input and likely also affects downstream targeted destinations. Third, renormalization occurs cyclically, a conclusion that is implicit in the first two consequences of this hypothesis, allowing both maximal learning and maximal recovery for learning to occur. Fourth, renormalization subserves behaviorally significant learning functions, those of maintaining neuroplastic and behavioral capacities. Extant studies supporting these predictions reveal the presence of sleep induced mechanisms that operate throughout the cortical and much of the subcortical domains. A key mechanism engaging renormalization, notably, is the slow oscillation, whose synchronized activity pervades the cortex and activates down selection according to spike timing dependent plasticity rules. Thalamic gating of afferent input appears to originate within thalamic nuclei, affecting the initiation of slow wave up states and frequency of the slow wave oscillation. Importantly, while the SHY hypothesis may be interpreted as a non-specific, globally directed process for renormalization of synapses that experience substantial neuroplastic change; that is, subserving a chiefly homeostatic role, other studies indicate that renormalization entails the targeted removal of behaviorally irrelevant or minimally relevant, learned information or responses that might otherwise distort learned behaviors. Hence, sleep appears to optimize interactive responsivity bimodally by strengthening a small subset of neuroplastically altered circuits and pruning away a much larger subset of non-specifically modulated networks; that is, learning and forgetting are biologically regulated functions enabling optimal adaptability to an ever-changing environment

Introduction

Perhaps no behavioral feature is more evident and more widely distributed, nor more sought after than sleep. Yet, it is for its distinctiveness that sleep has often seemed at odds with daily needs, where attention and responsivity are critical to survival.

Each time sleep occurs the ability to appraise the events around us is inevitably lost. This interruption of sensorial content represents a definitional and unique feature of sleep, one that distinguishes it from other behavioral states, all of which otherwise retain the ability to promptly respond to stimuli. The fact that humans and all other animal species require sleep, therefore, strongly indicates the existence of some fundamental physical and neural reason for it to occur; that is, sleep reveals the presence of some undetermined physical feature, which no other mechanism can respond to. Indeed,

the notion that sleep is vital is supported by the existence of various cognitive impairments associated with sleep deprivation [1-3]. In the most extreme case of sleep deprivation, fatal familial insomnia [4] for example, sleep is impossible, inevitably leading to death

One widely acknowledged proposal, the SHY hypothesis, links this essential function to neuronal properties evoked by centrally directed communication, which involve changes in the strength of interneuronal exchange at the level of the synapse. This hypothesis, termed the synaptic homeostasis hypothesis (SHY), privileges the unique ability of the brain to learn from external events of the world that become inscribed through neuroplastic changes in synaptic connections [6]. The SHY hypothesis proposes that these neuroplastic changes entail increases in synaptic potentiation, which can be visualized electrophysiologically in alterations of size and frequency of miniature end plate potentials. Because the extent of potentiation necessarily possesses an upper limit, there is a need to regularly reduce the level of potentiation so that the brain can continue to learn. This readjustment is proposed to occur during sleep [7].

Sleep, according to this model, is vital not merely for the restoration of exhausted resources but for preservation of the ability to successfully interact with the external world. Sleep therefore represents a preparative system that is essential for enabling organisms to optimally utilize sensorial information for survival. Mechanisms governing the events of sleep can thus be expected to regulate sensorial flow and recalibrate changes introduced by sensorial input that would lessen optimal responsivity during wakeful states.

This paper will first briefly review some extant models [7,8] on physical principles governing sensorium induced neuroplastic change and then examine how cortical activity during sleep depends on the constraints exerted by these principles. The paper will then explore how this dependence has led to the mechanisms that regulate sensorial flow into the cortex and that shape learned responses and the recovery of sensory-motor, neuroplastic capacity for future learning.

The Universal Need for Sleep – Renormalization and Neuroplastic Competence

The SHY proposal, that sensorium induced input asymptotically leads to a limiting level of synaptic potentiation, lays claim to the presence of a fundamental physical principle governing sensorium induced, neuroplastic change. There is considerable evidence that this physical principle is thermodynamic in nature. Ilya Prigogine, notably, first proposed that organisms occupy far from equilibrium highly ordered, entropic states that need to be sustained by ongoing free energy input. This he proposed based on the observation that living organisms were highly ordered structures that coexisted with a low order surround.

Extending Prigogine's analysis, Friston hypothesized that cognition itself was subject to free energy constraints that determined the level of entropic order in the brain, which he termed the free energy principle [8,9]. Ongoing informational flow from the sensorium was proposed to lead to a rise in the information related, state variable, entropy [10]. Like potentiation, entropy thus represented a saturable, though abstract, quantity driven by sensorial input toward some saturable level that was dictated by thermodynamic constraints.

Unlike the potentiation hypothesis, however, the free energy principle did not postulate a specific period devoted to recovery from synaptic change. Instead, the brain was proposed to counter ensuing information accumulation by optimizing behavioral patterns that minimized the need for future change. Inputs that occurred together more frequently than might be expected by chance, for instance, were 'registered' because they suggested regularities in the environment that were predictable. Once these 'coincidences' were detected, a neuron would communicate them to its target neuron, leading to synaptic strengthening, or potentiation. The effect of registering these 'coincidences' thus enabled the brain to structure its behavior in such a way as to minimize unexpected occurrences and guide the selection of behavioral responses on the basis of their likelihood. By such 'active inferencing' [11] the brain would come to reflect the regularities observed in the external world, an organizational arrangement that served to maximize free energy efficiency.

The free energy principle governing cognition thus resembled aspects of the SHY hypothesis in providing an explanation for changes in synaptic events that were due to sensorial input and that built on the brain's ability to enable the organism to better confront a continually changing, environmental landscape. Moreover, by staging causal optimization in terms of an entropic cost function the model accounted for some physical constraints that placed an upper bound on synaptic change. Nonetheless, while the free energy principle accounted for increases in a synapse related, saturable physical quantity – albeit an abstract one, it did not specifically address the attainment of saturability that is the result of ongoing sensorial novelty and that is inherent in the relentless circumstances occurring in the external world [12]. This relentlessness means that the persistence of novel input from the sensorium continues to generate synaptic reorganization and affect entropic order, despite causal inferencing that may act to diminish the rate of attainment of an overall entropic level. Faced with ongoing novelty, the organizational resources of brain synapses can thus be expected to approach saturation and operate within physical ranges that regularly encounter upper limits under the assumptions of both the SHY and free energy principle proposals. Indeed, the observation that all known animal species need to 'regularly disconnect' constitutes a strong argument that sensorial novelty is persistent and that its input repeatedly saturates a physical condition that must subsequently be replenished; that is, the brain is 'awash' in new experiences for which physical compensation is required.

Hence, sleep is the mechanism that has evolved to account for the cost of the physical events of neuroplasticity, which enable the organism to adapt and survive in a constantly changing environment [13]. When this cost is not accounted for cognitive function is poor. Acute and chronic sleep loss, for example, have pervasive negative effects on performance and many brain functions, including the

ability to learn, remember, speak clearly, judge risk, and understand complex information needed for decision making [2]. Physically, therefore, sleep assists in maintaining an overall balance of synaptic strength across brain circuits, which may be conceived as a synaptic renormalization. Both hypotheses thus predict that overall synaptic strength in the brain should not be balanced at all times, but instead be biased toward a net potentiation during the major wake period and toward a net depression during sleep [6].

Theoretical Implications of Current Sleep Models

This conclusion, drawn from two leading proposals describing the physical principles governing sleep mechanisms, has several implications. First, observable replenishment mechanisms should entail a sensorial disconnection from the external world in order that a process of renormalization occur; that is, renormalization should take place during unconsciousness. It has been argued for instance [6] that if the nervous system must acquire information about the environment to survive, such acquisition should be confined to periods of waking, when responsivity is maximal, rather than during sleep, when neural activity is at least partly disconnected from the external world" [7]. Second, such mechanisms should occur globally; that is, at a minimum they should be found in all brain domains having sensorial input. Additionally, neuroplastic changes should also affect downstream targeted destinations; that is, rather than modifying only brain regions receiving direct sensorial input, connectivity changes should be distributed across most domains of the brain. Thirdly, renormalization should occur cyclically, a conclusion that is implicit in the first two consequences of these hypotheses. Fourthly, renormalization should subserve behaviorally significant learning functions, maintenance of capacity and behavioral salience.

Disconnection from the sensorium entails molecular, ultrastructural, and electrophysiological phenomena

For excitatory synapses, which account for a majority of the synapses in the mammalian brain, the first prediction has received support from molecular, ultrastructural, and electrophysiological measures of synaptic strength [14,15,16]. At the molecular level, modifications in the strength of excitatory synapses have been shown to involve changes in the surface expression and subunit composition of the glutamatergic AMPA receptors, as well as phosphorylation and other post-translational changes that alter the open probability of these receptors and their ability to remain anchored to the membrane. Surface insertion of GluA1-containing receptors, and the phosphorylation of GluA1 at Ser831 and Ser845 by CaMKII and PKA, particularly, have been correlated with synaptic potentiation.

RNA-sequence analysis in the adult mouse frontal cortex, moreover, has revealed significant overlap of transcripts differentially expressed between acute sleep deprivation and sleep, and transcripts affected by the loss of the transcription factor myocyte enhancer factor 2C (MEF2C) [17,18]. Also found is a relative dephosphorylation of MEF2C after 6 h of sleep deprivation as compared to sleep, consistent with a wake-related increase in MEF2C transcriptional activity, as well as an increase in the frequency and amplitude of mEPSCs. Together, these findings point to a key role for MEF2C in mediating the response to sleep deprivation and the sleep-dependent decline in excitatory synaptic strength. Consistent with this, MEF2 transcriptional activity is activated in response to glutamate release and membrane depolarization, and the main effect of MEF2 activity in post-mitotic neurons is to constrain the density of dendritic spines and excitatory synapses. Many targets of MEF2, additionally, have been shown to be involved in synaptic weakening, including the genes Arc and Homer1a.

Electrophysiologically, experimental evidence supports distinct physical changes during wake or sleep periods that are reflected in spontaneous miniature excitatory postsynaptic currents (mEPSCs) in the rodent cortex. By the end of the wakeful period the amplitude and frequency of mEPSCs increase in the superficial layers of the rat and mouse frontal cortices whereas following recovery from sleep they decrease. Ultrastructurally, the increase in the former has been correlated with the synaptic insertion of calcium permeable AMPA receptors [19]. During sleep, this GluA1 synaptic expression decreases with a corresponding shrinkage of the axon-spine interface.

The global distribution of sleep mechanisms

A second implication of these proposals is that renormalization should occur globally; that is, if sleep is a consequence of enhanced synaptic strengthening, renormalization should occur in all brain regions where sensorial input causes neuroplastic change. Current evidence indicates that this is crucially dependent on neuronal activity, especially during NREM sleep, which comprises roughly 80% of all sleep time. New studies show that down selection is, surprisingly, a consequence of spiking activity involving several distinct electrophysiological signatures, including hippocampal sharp waves, ripples, and slow wave oscillations [20].

The organization of sharp waves and ripples appears to be mediated by the slow wave oscillation, which features prominently during NREM sleep. This slowly oscillating wave originates from the thalamus and cortex and oscillates roughly every second between an UP period of depolarization with spiking and a DOWN/OFF period of hyperpolarization with neuronal silence [21]. During non- REM (NREM) sleep, for instance, neural activity is observed in the EEG as a succession of K-complexes, sleep spindles, and slow waves. This defining feature of NREM sleep occurs roughly in synchrony across all neurons, allowing their pooled activity to be detected at the cortical surface as slow waves. This means that the slow oscillation is a global, synchronized network phenomenon, involving neurons throughout the cortex and, to a lesser degree, neurons in subcortical areas, including the thalamus, striatum, and cerebellum. Within the local cortical network (within a few tens of millimeters), cortical neurons synchronously depolarize and hyperpolarize during the slow oscillations.

Studies monitoring the distribution of selected slow oscillation phases reveal that the timing of the negative peak exhibits a continuous shift that can be traced spatially throughout the cortex [22]. On average, the maximum delay across the cortex, calculated by determining the difference between the negative peak of

the initial slow wave trace to the negative peak of the terminal trace is about 120 msec. Additionally, slow oscillations originate more frequently in anterior regions and propagate posteriorly. Streamline maps that condense the spatio-temporal dynamics of the slow oscillation display an origin density that coincides with the positioning of anterior electrodes, while the average delay map assumes a predominant fronto-occipital direction of propagation. Importantly, the pattern of origin and propagation of slow oscillations is reproducible across time and across subjects.

Taken together, these studies show that post-learning sleep occurs across the cortex leading to a slight increase in firing in a small set of neurons whose activity is causally linked to neuroplasticity learning, with an activity synchronized and much greater decrease in firing of a larger set of neurons not involved in neuroplastic modulation, consistent with the renormalization hypothesis.

The cyclical nature of sleep: circadian rhythms

A third implication of the current sleep hypotheses is the cyclical character of renormalization events, which are dictated by the ongoing twin needs of neuroplastic learning during wakeful periods and of replenishment during sleep. The temporal organization of these cycles is evident in their adherence to nature's light/dark rhythms, where the overall balance in total synaptic strength is maintained across the circadian 24 hour sleep/wake cycle with its temporally regulated, reoccurrence of similar events. Extant studies now reveal extensive details of these processes.

Based on the presence of this pattern, the fields of circadian biology and sleep-wake regulation have been closely allied for decades, with studies exploring how the circadian clock regulates daily rhythms in sleep and wakefulness, and in turn how arousal levels in animals affect their circadian clocks. Despite their close relationship, the two, nonetheless, are physiologically independent. Collectively, they may be understood as a homeostatic process – the plastic, organizational events of wakefulness and the dissociative, restorative events of sleep – and the circadian clock like mechanisms that temporally govern the distribution of wakefulness and sleep periods in synchrony with the external environment [23,24]. While the two systems have been shown to share elements of their mechanisms, in other aspects the two display many distinct features, evident in their anatomical, molecular, and electrophysiological details.

The preeminent circadian clock in mammals is located in the suprachiasmatic nucleus (SCN), immediately above the optic chiasm and juxtaposed with the third ventricle. Lesions of the SCN eliminate daily rhythms such as the sleep-wake rhythm [25]. The SCN circadian oscillator consists of a transcriptional-translational negative feedback loop (TTFL) involving a group of clock genes that includes Period (Per) 1 and 2; Cryptochrome (Cry) 1 and 2, Brain and muscle Arnt-like-1 (Bmal1), and Clock. While the SCN clock phase is modulated by many inputs, the primary environmental synchronizer is light stimulation via the retina, which is then relayed to the SCN. Circadian mechanisms regulating sleep include SCN efferents to the subparaventricular zone, which sends excitatory projections to the medial preoptic and dorsomedial hypothalamus, the latter of which sends additional excitatory projections to LH orexin neurons and to the LC. SCN neuronal activity is higher in the day, with initial excitatory output from the SCN in diurnal animals [26,27]. Distinct from the circadian signals emanating from the SCN, there are also distributed circadian influences on sleep. For example, the circadian clock gene Bmal1 regulates the rhythmic production of histamine in wake-promoting tuberomammillary neurons. Selective Bmal1 deletion in these neurons, notably, renders them arrhythmic. Another circadian clock gene, Reverbα, regulates circadian dopamine production in the VTA.

Unlike the SCN circadian clock, the sleep-wake system is distributed across many brain regions, including the brainstem, midbrain, hypothalamus, thalamus, and cortex. Moreover, sleep is composed of a complex mixture of different brain states, having their unique electrical recording features. Broadly these include slow wave sleep (SWS), characterized by high amplitude, low frequency brain waves and rapid eye movement sleep (REMS), defined by low amplitude, higher frequency EEG activity, with mixtures of these occurring during transitional phases. The nature of the homeostatic 'process' is less clear than that of circadian rhythms, and likely encompasses multiple factors. Examples of postulated molecules include extracellular adenosine, which has been shown to increase during wake in parallel with higher metabolic activity and to decrease during sleep as metabolism wanes [28]; prostaglandin D2, which also accumulates during wake, activates DP1 receptors and increases extracellular adenosine levels; and cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)α. Central to the concept of the homeostasis process is that sleep serves a restorative function that allows the brain to consolidate key synaptic changes generated by previous events, prune unneeded alterations, replenish energy stores, and eliminate accumulated metabolic byproducts. Although the circadian and sleep-wake systems are quite distinct, it is noteworthy that they share many cellular processes. Accumulating evidence supports both systems utilizing extracellular processes that overlap the synaptic mechanisms associated with learning, memory, and drug addiction, including changes in enzymatic activity and morphological changes [29].

Gating Afferent Input: Modulation of Global Up and Down States

The arousal system

The global impact of sleep on cortical activity and the necessity to rhythmically regulate afferent input implicate precise mechanisms that oversee transitioning between wakeful periods of interactive learning to sleep and from sleep to wakefulness. Extant studies have linked these mechanisms to the arousal system, so named for its role in transitioning from sleep to wakefulness.

Insight into these mechanisms has emerged from studies of trauma lesions in humans, pharmacological experimentation in mammalian species, and in situ preparations. Together, they have revealed a critical dependence of sleep like states on the modulation of arousal systems, with the inhibition of neurotransmitters like GABA leading to sleep and their stimulation to wakefulness. While these have to date been the primary mechanisms identified for transitioning between sleep stages, other work has also revealed

physiological mechanisms that act directly to induce sleep.

Characteristic of the trauma observations is the case of a 39-year-old man [30] who suffered head trauma resulting from a car collision. Immediately after the head trauma incident, the patient complained of excessive sleepiness and sudden muscle weakness of all four extremities. At three months after onset, his Epworth Sleepiness Scale score was 19, which has a normal range of 10. Diffusion tensor imaging data of the ascending reticular activating system (ARAS) showed that the tract volume of the right ventral lower ARAS was substantially decreased compared with control subjects indicating neural trauma to the structure at the site between the pontine RF and the hypothalamus, thus revealing the involvement of the ARAS in sleep modulation.

Consistent with such trauma observations, data from many laboratories has demonstrated that GABAergic transmission in the PnO promotes wakefulness [31]. Inhibiting GABAergic transmission in the PnO by microinjection of the GABA synthesis inhibitor (3-MPA), for instance, decreases anesthesia induction time with isoflurane and/or propofol. Elevating GABA levels with the uptake inhibitor (NPA) into the PnO reverses this effect. On the other hand, modulation of GABA levels in the PnO does not alter the time to recovery of anesthesia. These data provide support for the conclusion that modulation of arousal is a primary mechanism for transitioning between sleep stages, while the lack of effect on the emergence from anesthesia implicates a more complex process for this aspect of arousal than GABA modulation alone.

In addition to GABA, the peptides hypocretin-1 and -2, termed orexin A and B, also modulate sleep stage transitioning via the arousal system [32]. As in the case of GABA receptors, receptors for the hypocretins are site specific and widely dispersed. Cell bodies of hypocretin-producing neurons have been localized to the dorsolateral hypothalamus but send projections to all the major brain regions that regulate arousal. Hypocretin-1 delivered to the rat dorsal raphé nucleus increases serotonin release in the dorsal raphé and to the pontine nucleus increases acetylcholine and GABA levels, suggesting that the peptide may broadly activate distinct neurotransmitter release as a function of brain location.

Few studies have revealed a direct induction of sleep via neurotransmitter up regulation. Of these, REM sleep was induced in rats using vasoactive intestinal polypeptide (VIP). A closely related peptide, the pituitary adenylyl cyclase-activating polypeptide (PACAP), was even more effective [33]. The IC50 for PACAP was 2.4 and 3.2 nM, for example, as compared with VIP IC50 > 1 mM suggesting the peptide has a highly specific and effective role in the induction of REM sleep regulation. In an interesting observation, injection of PACAP into the PnO generated REM sleep lasting 11 consecutive days.

Gating of sensorial Influx – the slow oscillation and thalamic regulation

While the arousal system enables the transitioning between sleep and wakefulness, other mechanisms needed to prepare the brain's synaptic organization for confronting daily interactions must become active throughout the sleep phases. A key postulate of current sleep models, for instance, is the restorative effect of sleep on learning in brain areas that have experienced heavy neuroplastic changes during wakeful periods. This postulate was tested in experiments that focally perturbed deep sleep in the motor cortex and investigated the consequences on behavioural and neurophysiological markers of neuroplasticity related to motor practice. The restoration in the ability to learn was markedly attenuated in these experiments when slow waves were selectively perturbed in the motor cortex [34].

This and a growing body of evidence reveals that among the key mechanisms evoked for renormalization is the slow oscillation that is observed during slow wave sleep (SWS). Besides organizing and synchronizing several brain activities, like sharp wave ripples, the slow wave displays unique up and down activity states affecting neurons throughout the cortical regions that help to reprime cortical neurons. During the slow oscillation, most neurons show periods of suprathreshold depolarization, alternating with periods of relative inactivity, the so called Up and Down states associated, respectively, with barrages of synaptic inputs during active periods and the withdrawal of these inputs during inactivity. Of the two periods the UP states alone appear to contribute to renormalization. During the ON/UP states of the slow oscillation optogenetically introduced, experimental inhibition that reduces firing of the SWS prevents post-sleep improvement in neuroprosthetic learning [20]. When such optogenetic manipulation occurs during the DOWN/OFF periods alone no effect is observed.

According to the widely accepted spike timing dependent plasticity (STDP) rules, presynaptic activation can lead to either no change in synaptic strength, synaptic depression (diminished synaptic response), or synaptic potentiation depending on the absence, presence, or relative coincidence of timing of postsynaptic spiking. During the UP states of the slow oscillation, a strong bias toward synaptic depression is observed. Specifically, after stimulation of layer 4 to layer 2/3 connections, synaptic strength never significantly increased and remained unchanged when presynaptic activation was quickly followed by postsynaptic activity. When postsynaptic activity either preceded presynaptic activation or followed it at long intervals it decreased. This synaptic depression associated with the UP states was mainly observed in young animals although smaller levels could still be seen in older mice [20]. The presence of synaptic depression during the slow oscillation could explain how sleep could result in diffuse but synapse-specific synaptic renormalization: synapses strengthened during wake, as well as those that are most coherently reactivated during sleep, would be more likely to show coincident firing during the UP states and thus be protected from synaptic de- pression [35] whereas a much larger group of neurons activated asynchronously would experience depression and become renormalized.

Similar to the events of slow wave induced depression and despite a broad consensus that SWRs are likely candidates for inducing synaptic potentiation, recent studies have shown that SWRs also promote synaptic weakening rather than potentiation [20]. Consistent with these results closed-loop optogenetic inhibition of SWRs prevents the decline in the slope of hippocampal fEPSPs that normally occurs in sleeping mice. Conversely, a recent study showed that SWRs also promote synaptic weakening [36].

The authors first replicated a previous finding that SWRs become more frequent after spatial learning. Then they showed in vivo in adult mice that closed-loop optogenetic inhibition of SWRs prevents the decline in the slope of hippocampal fEPSPs that normally occurs in sleeping mice. The authors also took advantage of an in vitro model of SWRs, obliquely cut hippocampal slices, which spontaneously emit SWRs. As in vivo in adult mice, in these slices taken from adolescent mice, the occurrence of SWRs led to a progressive decline in the fEPSPs slope that could be blocked by optogenetic inhibition of SWRs. By contrast, the fEPSPs did not decline in horizontal slices that lacked SWRs. Two-photon imaging also showed that the head size of most CA1 spines decreases with time in spontaneously emitting SWRs slices. The decrease occurs in thin and stubby spines but not in rounded spines.

Significantly, sleep-dependent renormalization seems to spare those neurons and/or synapses that are most active during sleep. It is well established, for example, that neurons activated during exploration and learning are preferentially reactivated with a similar sequential pattern of firing during SWRs, while disruption of SWRs impairs memory, suggesting that they play an important role in its consolidation.

Thalamic sensory gating and slow wave modulation

To avoid the obvious conflict with renormalization that would accrue with ongoing afferent input, sensory input must be subject to termination throughout the renormalization phase. Mechanisms for such gating have yet to be confirmed, but numerous studies suggest that there is significant influence from thalamic nuclei in suppressing afferent input. For example, recordings from various thalamic nuclei suggest that thalamocortical neurons may participate in processes beyond that of initiating the onset of each slow oscillation cycle. Contributions from sensory thalamic nuclei via the relay cells, including the ventral posterior medial nucleus and the lateral geniculate nucleus, are strongly inhibited, thus preventing spiking at nearly all times except at the onset of the Up state. By contrast, excitation is dominant in neurons within non-sensory thalamic nuclei, including the posterior nucleus and the intralaminar nuclei. Their continuous activity permits their neurons to spike throughout the duration of the Up state [37]; that is, activity originating primarily from non-sensory nuclei.

Firing patterns appear to originate through the inhibition of sensory thalamic nuclei by the thalamic reticular nucleus (TRN) together with a corresponding lack of inhibition in non-sensory thalamic nuclei, which receive the majority of their inhibitory input from the zona incerta [38]. In particular, TRN neurons that project to sensory thalamic nuclei display high activity during the slow oscillation, while those with projections to limbic thalamic nuclei have relatively low activity [39]. This means that excitation from non-sensory thalamic nuclei, are likely to have the greatest influence on Up state initiation, as well as its persistence Indeed, the prolonged excitation of thalamocortical neurons by non-sensory thalamic nuclei during Up states, suggest that these neurons are likely to suppress most afferent influence into the cortex in addition to assisting in synchronizing the slow oscillation throughout cortical regions.

Besides gating afferent input, these thalamic nuclei also appear to modulate slow wave features during UP states. It is known, for instance, that sensory stimulation or direct thalamic stimulation of the cortex stimulates cortical activity under various circumstances, indicating the evident capability of the thalamus to evoke Up states. In anesthetized animals, for example, both prolonged sensory stimuli, such as drifting gratings [40] or whisker deflections in rodents [41] are effective initiators of Up states in the respective sensory cortices. Also, electrical or optogenetic stimulation of the thalamus in slice preparations containing axons of thalamocortical neurons [42] can cause Up states [43,44]. Burst-firing of thalamocortical neurons has been shown to occur prior to the discharge of cortical neurons during the Up state of the slow oscillation, while severing thalamocortical axons in the mouse barrel cortex in vitro substantially decreases the frequency of the slow oscillation. Together, these data show an active contribution of thalamic input to the initiation of spontaneous Up states.

In addition to the initiation of Up states, thalamic input also modulates its duration. Recent in vivo studies, for instance, have demonstrated an important contribution of thalamic activity to the pacing of the slow oscillation. Acute pharmacological blockade of action potentials in thalamic neurons in anesthetized and naturally sleeping rats decreases the frequency of the slow oscillation [45] an effect that may be due to blockade of T-type Ca2+ channels, which have been shown to significantly reduce slow oscillation frequency.

Using the anesthetized cat, in vivo preparation, thalamic inactivation reduced both the slow oscillation frequency and the synchronization of Up states in concurrently recorded, cortical neurons [46]. In some recordings, slow oscillations were virtually abolished following thalamic lesions. Interestingly, these continuous recordings revealed that while the slow oscillation frequency changed immediately following the lesion, remaining significantly lower up to 12 h following thalamic inactivation, they then regained a frequency comparable to the sensory input state within 30 h. These results suggested that the regaining of normal slow oscillation frequency entailed changes in excitatory synaptic connections, and therefore internal circuitry adjustments that occurred due to thalamic influence. Hence, the thalamus appeared to affect the slow oscillation not only at its initiation, but also throughout its duration, an influence that apparently resulted in cortical, microcircuit alterations.

Future Directions in Sleep Investigation: Renormalization and the Behavioral Role of Forgetting

A key postulate of the sleep models is the restorative effect of sleep on learning in brain areas that have experienced heavy neuroplastic changes during wakeful periods. As mentioned, this postulate presumes that neuroplastic change is saturable and that the physical substrate for this change is substantially altered by sensorial activity, thereby diminishing the available neuroplastic learning capacity for future behavior. Indeed, the influence of afferent input on circuit neuroplasticity is relentless, suggesting that much of what is learned is either useful only for a narrow window of time or even superfluous. Much of this sensorial input

is known to subserve motor or motor related activities, which are, typically, often of short duration. Accordingly, a fourth prediction that is implicated by these models is the need to selectively prune unneeded neuroplastic change, which would prevent future learning and could distort previously learned behaviors.

Motor and motor related activities

In a contemporary understanding of motor activity, afferent induced, neuroplastic change is likely to be evoked at three levels: as a direct response to environmental conditions; as a hypothetical response to perceived intentional action; and in the integration of bodily actions, generated, for example, in constructs like the motor image. Insight into these levels of neuroplasticity emerge from the widely accepted Gibson theory of perception, which takes the relationship between the perceiving system and its environment as primary [47,48]. In so doing, it places the significance on motor activity for its ability to inform the system and to structure perception based on specific motor activity in the world. Notably, the mind perceives the world in terms of the various activities it affords to the body; hence, sensorial input is related to multiple affordances that the body may potentially engage in through motor activities. Perception thus subserves action, which is constrained by the bodily format that dictates which motor actions may be taken, a conception reflecting embodied constraints on environmental interaction. Hence, neuroplastic, sensorium induced change, in the Gibson understanding of perception, is considerably greater than the learning entailed solely in intentionally selected and explicit, interactive motor responses to external events. In principle, this conception places extraordinary computational requirements on the brain during acute phases of performance and responsivity [49].

Renormalization and forgetting

Accordingly, while the SHY hypothesis may be interpreted as a non-specific, globally directed process for renormalization of synapses that have experienced substantial neuroplastic change; that is, subserving a chiefly homeostatic role, renormalization undoubtedly also entails a behaviorally significant, targeted removal of irrelevant or minimally relevant, learned information or responses that may compromise access to key learned or future behaviors. This is to say that even though forgetting is often thought of as a failure or limitation of the brain, these recent studies reveal that forgetting is likely to have acquired a biologically significant functional role, allowing optimal adaptability to an ever-changing environment [50]. Indeed, the vast number of interactive circumstances and predictive models engaged in by the brain, suggest that, behaviorally, most will be of short duration.

Hence, forgetting neither appears indiscriminate nor passive, but rather active and targeted, entailing erasure of synaptic structure that has acquired an enhanced configuration or, in cases, wholesale removal, which is to say synaptic weight down- scaling or elimination [7]. Renormalization, therefore, is likely to be highly structured, with refined mechanisms for operating bimodally, preserving a vast cognitive structure through the retrieval of learning capacity or the retention of key constructs that are then refined to assure their operational salience when implemented.

Conclusion

This review has focused on how the intersection of physical factors – thermodynamic and circuit driven - and the need to preserve learned behaviors for successfully negociating the world have shaped the neural architecture of sleep. This relationship emphasizes the fundamental role played by thermodynamic constraints, dictating such features of sleep as global distribution, timing of occurrence, and regulation over afferent input. However, this relationship also reveals how the constraints imposed by thermodynamic are not only accommodated but superceded, allowing the organism to address critical needs required for viability and well-being.

In addressing these needs organisms have attached singular importance to learned behaviors, assisting them in overcoming the capacity limitation attained by neuroplastic change while learning and assuring that ongoing learning retains the specificity needed for successful interactive outcomes. Indeed, the role of sleep for forgetting seems to be entirely unique and cannot be substituted by any other state. Sleep thus functions not only for remembering, but, more significantly, for assuring that learned behavior retains its relevancy for survival.

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Conflict of Interest

No conflict of interest.

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