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Cortical Neuronal Mechanisms of Sleep Homeostasis

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The longer we are awake, the deeper is our subsequent sleep. On the other hand, the shorter and more fragmented is our sleep, the more difficult it is for us to maintain wakefulness and stable cognitive performance the next day. This relationship between wakefulness and subsequent sleep becomes especially apparent after sleep deprivation or during chronic sleep restriction, which is experienced by millions of people in our society, as well as in multiple neurological, respiratory and other chronic diseases. Invariably, poor sleep leads to fatigue, sleepiness, marked cognitive deficits and impaired mood. The crucial question is what happens to the brain after a period of being awake or asleep, and where in the brain and why do these changes occur. This review summarizes information about neurophysiological substrates of sleep homeostatic processes at the cellular and network levels. It is suggested that sensory, behavioral and cognitive deficits after sleep deprivation resulting from the imbalance between local and global neuronal interactions can be reversed only by physiological sleep.

Keywords: *sleep, waking, sleep homeostasis, neocortex, sleep deprivation, EEG, slow waves.*

КОРКОВЫЕ НЕЙРОННЫЕ МЕХАНИЗМЫ ГОМЕОСТАТИЧЕСКИХ ПРОЦЕССОВ СНА

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Известно, что чем дольше мы бодрствуем, тем глубже наш последующий ночной сон. С другой стороны, чем короче и более фрагментирован наш сон, тем сложнее на следующий день поддерживать устойчивое бодрствование и успешную когнитивную деятельность. Эти отношения между сном и последующим бодрствованием после депривации сна или хронического недостатка сна наблюдаются как у миллионов здоровых людей, так и при различных хронических заболеваниях. Недостаток сна является причиной возникновения состояния утомления, повышенной сонливости, когнитивных расстройств и ухудшения настроения. Фундаментальный вопрос современной нейробиологии: что происходит с мозгом после длительного периода бодрствования и отсутствия сна и в каких областях мозга, когда и какие изменения происходят? Настоящий обзор обобщает информацию о нейрофизиологическом субстрате гомеостатических процессов сна на клеточном и нейросетевом уровнях. Выдвинуто предположение, что сенсорные, поведенческие и когнитивные нарушения, наблюдаемые после депривации сна, возникают в результате дисбаланса между локальными и глобальными нейронными взаимодействиями, которые могут быть нормализованы только в процессе физиологического сна.

Ключевые слова: *сон, бодрствование, гомеостаз сна, кора головного мозга, депривация сна, ЭЭГ, медленные волны.*

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Throughout the life span every animal spontaneously goes through a sequence of distinct behavioral and brain states. One subdivision of these states is in wakefulness and sleep. Sleep is a heterogeneous state, subdivided into non-rapid eye movement (NREM) sleep, also called slow-wave

sleep, and REM sleep. Waking is also anything but a steady state, varying on a time scale of hours, minutes or even seconds from attentive alert state to a largely disconnected from the environment state of restful drowsy waking. However, the activity of the brain does not only reflect the current level of arousal, ongoing behavior or involvement in a specific task, but also is influenced by what kind of activity, and how much sleep and waking occurred previously. Indeed, being awake and asleep do not alternate at random, but preceding sleep-wake history and the circadian clock govern the global and local changes in brain state [10, 43]. For example, prolonged waking is invariably followed by deep restorative sleep, while NREM sleep episodes alternate on a regular basis with REM sleep periods. The duration and quality of waking predicts subsequent sleep intensity, reflected in high-amplitude electroencephalography (EEG) slow waves (slow-wave activity, SWA), arising from synchronous fluctuations of the membrane potential in large neuronal populations [77].

The classical neuroscience view is that brain states are regulated in a global fashion by a set of subcortical neuromodulatory nuclei, projecting to the thalamus and widely across the neocortex and/or modulating the activity of each other [39]. However, evidence has accumulated that neither wake nor sleep are always global [43]. When we zoom-in on the activity of individual cortical neurons and neuronal populations, we see that while some neurons are irregularly active (ON), as is typical for waking, others may stay silent (OFF), as during sleep, even when the animal is behaviorally awake, and vice versa [92, 93]. Evidence derived from this new approach implies a crucial role for sleep in neural plasticity, local synaptic recovery processes and, ultimately, cognitive function. Interestingly, it was found that specific behaviors or peripheral stimulation during waking results in local, use-dependent changes in sleep EEG SWA, when some cortical regions "sleep" more intensely than others, depending on their preceding activity [43, 88]. Such changes may arise at the level of cortical neuronal circuits, as it has been shown that early intense sleep, when slow waves are large and frequent, appeared to be associated with short, intense neuronal ON periods, alternating frequently with relatively long OFF periods [92, 93]. Moreover, staying awake does not only lead to intense subsequent restorative sleep, but also to specific changes in the wake EEG and cortical neuronal firing [47, 92, 93, 96], which might underlie the well-known psychomotor and cognitive deficits typical for sleep deprivation [26].

Surprisingly, while homeostatic regulation of sleep is a precise, ubiquitous and basic phenomenon found in all animals species studied up-to-date [81], its underlying mechanisms are still unknown. There are several candidate mechanisms which are believed to be implicated in sleep need. Among those are regulation of brain metabolism [65], activity-dependent release of cytokines [61] or synaptic plasticity [43, 82]. Several specific questions remain unanswered and should become the primary targets of future research. It is unclear at what level sleep-need accumulates and where sleep is initiated: e.g. individual neurons, local or distributed neuronal populations, cortical or subcortical regions, or specific neuronal subtypes? Moreover, it is still unknown which molecular, cellular and network mechanisms underlie the need for sleep, and what happens in the brain during waking that necessitates the occurrence of sleep. Finally, very little is known about how the changes in brain activity incurred during normal waking or sleep deprivation translate in the well-known behavioral and cognitive deficits.

1. BRAIN ACTIVITY IN WAKING AND SLEEP

A fundamental difference between wakefulness and sleep is the extent to which the brain is engaged in the acquisition and processing of information. In all species carefully studied so far, waking and sleep alternate on a regular basis and continuous wakefulness never lasts spontaneously for more than several hours or a few days [81], suggesting that sleep is necessary and it serves a vital role. The maintenance of waking and sleep states is regulated by the activity arising from several subcortical structures in the brainstem, hypothalamus and basal forebrain, which provide neuromodulatory (such as monoaminergic, glutamatergic, GABAergic and cholinergic) action on the neocortex [39]. Importantly, the same neuromodulatory systems are crucially involved in attention, cognition, behavior and many other aspects of the regulation of internal states and the interaction of the brain with the outside world.

The behavioral or vigilance state of an animal is usually reflected in the cortical electroencephalogram (EEG). Wakefulness in rodents is traditionally distinguished from non-rapid eye movement (NREM) sleep by the virtual absence of large-amplitude EEG slow waves, and by the presence of theta (~7–9 Hz) activity [98], pre-

sumably arising as a result of physical spread of theta activity from the hippocampus [32, 98]. Hippocampal theta activity has been related to voluntary activity, arousal, attention, the representation of spatial position, learning and other behaviors or functions [15, 32, 62]. Based on phase-analysis and pharmacological studies it has been postulated that there is more than one generator and more than one type of theta activity in the hippocampus [68]. The functional significance of hippocampal theta activity is still unclear, but it can be highly relevant for various aspects of behavior and cognition given the complex interactions between the cortex and hippocampus during sleep and waking [11, 14, 71]. Apart from the EEG, the activated pattern of brain activity during waking is also apparent at the level of firing of cortical neurons. Overall, neuronal discharge in waking is largely fast and irregular, although it is determined strongly by behavior and involvement in specific tasks. The cortical activity in awake animals is generated not only by ascending influences from specific wake-promoting areas [39] and intracortical and cortico-subcortical interactions [12], but also by behavior [64, 95] and processing of incoming external stimuli [72].

Cortical neuronal firing patterns in wakefulness and another activated state, rapid eye movement (REM) sleep, are profoundly and characteristically different from those in NREM sleep [77]. Cortical neuronal firing activity is generally slower in NREM sleep compared to both wakefulness and REM sleep [59, 77]. Moreover, independent firing of neurons in wakefulness is replaced with regular synchronous bursts of action potentials during sleep [59]. During NREM sleep the neocortex is functionally disconnected from the surroundings (environment), and the most distinctive feature of the EEG is the near-synchronous occurrence of slow waves in all or most cortical areas [53]. The fundamental cellular phenomenon underlying sleep EEG slow waves is the slow oscillation, comprised of a depolarized UP state and a hyperpolarized DOWN state, during which the cortical cell ceases firing [4, 25, 77]. *In vivo, in vitro* and *in computo* evidence indicates that the DOWN state of the slow oscillation is the result of disfacilitation (i.e. a lack of synaptic input), rather than of active inhibition [35, 76, 79]. The global cortical pattern of activity in NREM sleep consists of an alternation between periods of elevated neuronal firing (ON periods), lasting several hundreds of milliseconds, and shorter periods of generalized silence, corresponding to the negative phase of surface EEG slow waves. However, while it is well known that brain activity is different depending on whether you are awake or asleep, less is known about whether and why there is a difference in brain activity depending on for how long you have been awake or asleep before.

2. PRECEDING HISTORY: GLOBAL AND LOCAL REGULATION OF SLEEP

The function of sleep is likely to be closely related to sleep regulation. It is well known that sleep is regulated homeostatically [9], e.g. sleep loss is compensated by subsequent sleep intensity. In most species, sleep pressure increases as a function of time spent awake and decreases in the course of sleep. The best characterized physiological indicator of sleep-wake history is the level of cortical EEG slow-wave activity (SWA, EEG power between 0.5 and 4.0 Hz) during NREM sleep [9]. In mammals, sleep SWA is high in early sleep and after sleep deprivation, when sleep pressure is increased physiologically, and decreases progressively to reach low levels in late sleep [80, 87]. The prevailing view is that brain states are regulated in a global fashion. However, evidence has been accumulated to indicate that neither wake nor sleep are always global [43]. Over the last two decades multiple studies have shown that during spontaneous sleep SWA is not uniform across the cortical surface, but shows topographic gradients. In both humans and animals, SWA is more intense in the frontal derivations, especially in early sleep or after sleep deprivation [17]. Moreover, peripheral stimulation or the spontaneous use of circumscribed cortical areas leads to more intense local EEG slow waves [40, 88, 97]. Such observations suggested that not only waking duration per se, but also specific waking activities affect the intensity of subsequent sleep, and indicate that sleep may play a local restorative function. Surprisingly, while sleep homeostasis is a precise, ubiquitous and basic feature of sleep in mammals and birds, the specific mechanisms underlying the sleep regulatory processes remain unknown.

3. TOOLS TO INVESTIGATE SLEEP REGULATION: FROM THE EEG TO NEURONAL ACTIVITY

Traditionally, sleep and waking in animals and humans have been investigated using EEG. The advantages of the EEG technique are that the signals, recorded with macroelectrodes placed on the skull or on the surface of the cortex, represent

large-scale cortical activity and that the recordings can be performed simultaneously from several cortical areas, and for many hours. Chronic sleep EEG recording and analysis led not only to the discovery that sleep consists of two different stages – NREM sleep and REM sleep, but also that sleep is regulated homeostatically, as manifested in an increase in sleep EEG slow-wave activity (0.5–4 Hz) after waking and its gradual decline across the night [10, 81]. However, there are also some limitations to the EEG-approach, such as volume conduction, poor spatial resolution and often the impossibility to trace the origin of EEG waves or their spatiotemporal dynamics to specific cellular and network mechanisms.

These shortcomings were partially resolved by single-cell electrophysiology, which was crucial in establishing a relationship between intracellular neuronal states, cortical neuronal activity and EEG/LFP waves (local field potential) [20, 77]. While this approach has proven essential for our understanding of how individual neurons change their activity in relation to behavior and vigilance states, it has also some significant limitations. Specifically, intracellular recording techniques do not allow long-term stable recordings in freely-moving rodents to be recorded, and even in head-restrained or anesthetized animals it is possible to record only a few cells at a time [20].

In order to investigate the mechanisms underlying homeostatic sleep regulation, a technique is necessary that on the one hand allows long-term stable recording in freely-moving, unanaesthetized animals to be collected, and on the other has sufficient temporal and spatial resolution to resolve spiking activity of individual neurons. Extracellular multisite recordings of large neuronal populations, together with local field potentials with microwire arrays or laminar probes [16], appear an ideal tool to bridge this gap between the EEG and intracellular single-cell recordings. Specifically, this technique is uniquely suited for investigating cellular and network mechanisms underlying local and global sleep regulation and the link between cortical neuronal activity and behavior.

4. SLOW WAVES, THEIR ORIGIN AND PROPAGATION

The patterns of neuronal and network activity are dramatically different between sleep and waking, and are also modulated by preceding history. This notion suggests that specific activity patterns typical for sleep may be causally involved in shaping cortical circuits by actively changing their morpho-functional properties. However, in order to understand the mechanisms by which the cortical neural dynamics affects functional connectivity between local and global neuronal assemblies, it is necessary to get insight into the cellular and network mechanisms underlying the major sleep oscillations.

The EEG during NREM sleep is characterized by high-amplitude slow waves that are abundant in early sleep and decrease in amplitude and number across the sleep period. As was mentioned earlier, the fundamental cellular phenomenon underlying the EEG slow waves is the cortical slow oscillation consisting of an UP state, characterized by sustained neuronal depolarization and irregular firing, which is followed by a hyperpolarized DOWN state during which every cortical cell ceases firing due to disfacilitation [4, 76]. It is currently under debate whether cortical slow wave activity has a functional significance or is just an epiphenomenon of some hidden processes. Apart from the function of the slow oscillation *per se*, several other questions remain to be addressed, such as what determines the characteristic regular occurrence of slow waves as a sequence of UP- and DOWN-states, whether and how this activity originates locally or can be triggered from outside, and how the activity propagates across the neocortex and why it does.

It was found that the slow oscillation can occur spontaneously in deafferented cortical slabs of a sufficient size [78]. The original notion that during sleep distant neurons fire more synchronously during the bursts of activity interrupted by the period of silence [59], was followed by a consistent observation that neuronal activity linked to EEG slow waves originates in a certain location and propagates to the neighboring areas in a three-dimensional pattern [84]. For example, it has been reported early on that both slow waves and neuronal activity from visual area occur always later than those from the association cortical areas [18]. In sleeping humans, high-density EEG showed that spontaneous slow waves originate predominantly at the anterior cortex and propagates over the scalp at a speed of ~1.2–7.0 m/s [53]. The UP states *in vitro* originated from cortical layer 5 and were recorded from the superficial layers with an ~10–30 ms delay [70]. Notably, the cortical traveling waves (rev in [37]) may not only originate spontaneously but can also be triggered by local electrical [78, 90, 91] or pharmacological [70] stimulation. It was proposed that the rate of propagation of slow oscillation is determined in

large part by the time required to bring each successive neurons to spike threshold [70]. Importantly, it was shown *in vitro* in barrel cortex that not only local cortical, but also thalamic electrical or pharmacological stimulation is able to recruit cortical ensembles into UP states indistinguishable from spontaneously occurring UP states [51].

The functional significance of slow wave propagation remains unclear. It is possible that the traveling wave represents a wave of recruitment of cortical areas into the same cycle of slow oscillation [67]. The rates of such recruitment may be determined by strength of synaptic connections that changes as a result of preceding sleep-wake history [28, 94]. It was suggested that UP states propagate by spreading from a specific focus [53, 70] or by synchronization of weak activity, originating at multiple locations [53, 78, 85]. Direct cortico-cortical connections are likely to play an important role in such propagation as the latencies were invariably shortest to the contralateral homotopic areas connected to the origins by the direct callosal excitatory fibers [21]. Thus, the activity of cortical neurons is driven not only by a local intracortical network but also by distant neurons from homotopic regions of the contralateral hemisphere [21]. Moreover, synchronization of the slow oscillation requires integrity of cortico-cortical connections as has been demonstrated with pharmacological and surgical tools [66]. The neurons located in supragranular cortical layers may play a critical role for such large-scale intracortical interactions, as they modulate, directly and indirectly, both excitatory and inhibitory synaptic interactions between cortical columns. A large proportion of excitatory synapses come from neurons located in other cortical columns by means of horizontal connections. It was shown that the EPSP amplitudes mediated by the layer *II/III* to layer *II/III* connections are significantly larger than those by the layer *V/VI* to layer *V/VI* connection [36] and, importantly, the propagation of excitation along supragranular layers does not require integrity of the infragranular layers [44]. Such long-range connectivity is crucially important for the balance between mostly inhibitory local connectivity and distant excitatory inputs [73]. Simulations showed that a net decrease in cortical synaptic strength leads to a reduced amplitude of cellular slow oscillations and to a marked decrease in network synchronization. In turn, these changes result in reduced slow waves in the simulated LFP [28]. Efficient mechanisms of intracortical synchronisation are crucially important for shaping cortical network oscillations [92]. It was proposed that the periodicity of the slow oscillation is determined by the balance between the recurrent excitation and inhibition in cortical networks [70]. However, it is currently unknown what determines the frequent occurrence of the large amount of high-amplitude slow waves under high sleep pressure condition, and what relevance does it have to the cortical function.

5. HOW DOES THE NEOCORTEX INTERACT WITH ITSELF AND WITH THE OUTSIDE WORLD DURING SLEEP

An essential function of the brain is to perceive complex external and internal stimuli and translate them in adequate behavioral responses. Fast and adequate response to incoming stimuli is on the one hand vital for survival but on the other hand is highly energy-demanding [7]. Therefore, continuous regulation of brain states is crucial for achieving a fine balance between speed, selectivity and economy in the interaction with the outside world.

Various aspects of behavior, brain state and network activity account for the trial-to-trial variability in the responses to stimuli [6, 30]. Important determinants of neuronal responsiveness are preceding activity [1] and the levels of neuromodulators that vary with the activity state of the brain [57] and impose both a global and a local, synapse-specific control [46, 52]. For example, evidence in several animal species indicates that the amplitude of various components of evoked potentials of different modalities is higher during slow wave sleep compared to waking or REM sleep [34, 83, 89]. It was found that in sleep or quiet wakefulness in different animal species the stimulation of various modality or location leads not only to the early mono- and polysynaptic components, but, later, to an emergence of a large-amplitude potential with a duration between 100–200 ms [83, 89]. Such a component may be associated with suppressed multiunit activity [83], diminishes during locomotor activity [27] and resembles the slow inhibitory potential triggered in cortical slices *in vitro* [55]. Also in humans the later components of ERPs are usually unique for sleep, possibly arising from a massive synchronized firing of the large number of presumably cortical cells [22]. The difference in the responsiveness to stimuli between wake and sleep [34, 53] can be accounted for by neuronal bistability, manifested in an alternation between periods of neuronal UP and DOWN states [35, 56].

The mechanisms underlying the cortical bistability, let alone its function are unclear. A bistability between UP and DOWN periods could be triggered by decreasing levels of arousal-promoting neuromodulators, which trigger leakage potassium currents and upregulate intrinsic currents and synaptic conductances [35]. Indeed, increasing sleep pressure can be counteracted in part by potentiating the action of neuromodulators through endogenous circadian influences [26], by direct stimulation of ascending systems [8], by pharmacological means (e.g. caffeine [45]), or by motivation [38]. An intriguing possibility remains that neuromodulation is not a global phenomenon but can occur in a local or modular fashion. For example, local cortical release of acetylcholine [46] or catecholamines [52] *in vivo* can be modulated presynaptically by cortical activity. Moreover, individual neurons within the locus coeruleus or cholinergic neurons in the basal forebrain do not always discharge in tight synchrony [60], suggesting that, at least in theory, they may impose independent or localized neuromodulatory effects on cortical activity. In turn, local changes in the level of neuromodulators could increase or decrease the probability of the initiation of local cortical slow oscillation [20, 78].

While the function of local or global neuronal bistability is unclear, it is well established that it dramatically affects the way neurons respond to their inputs. Specifically, it has been shown that cellular properties and the ability of neurons to generate spikes in response to stimulation differ not only between sleep and waking but also within sleep between the hyperpolarized and the depolarized state. Studies in the rodent somatosensory system showed that action potentials and postsynaptic potentials to brief whisker stimulation are largest and most reliable when evoked from down states [64]. On the other hand, in humans the amplitude of the auditory evoked response increased along the negative slope of the EEG slow wave and decayed during the positive slope [54]. Finally, *in vitro*, spontaneous occurrence of the upstate of the slow oscillation markedly diminished the evoked response to the glutamate, if it was applied immediately after [70]. Moreover slow waves, induced by local cortical electrical stimulation, were virtually absent if the stimulus was delivered immediately after a large spontaneous slow wave [91]. As a consequence, the evoked slow waves were large at the beginning of each NREM sleep episode but decreased in amplitude as sleep deepened [91], consistent with the fact that in both humans and animals EEG slow wave activity, which ultimately reflects the occurrence of high-amplitude slow waves, also builds up gradually within each NREM sleep episode [2, 86]. The differences in the neuronal responsiveness between UP and DOWN states might arise from the changes in various cellular properties, such as the fluctuations of the input resistance [23]. Thus, during the awake state the membrane potential is tonically depolarized and does not exhibit overt, rhythmic slow oscillations [33]. It can be hypothesized that the dramatic differences between the different phases of the slow oscillation in terms of responsiveness might also be a direct consequence of the difference in the ability to produce a synchronous response across large neuronal population.

It is well known that neuronal excitability is strongly correlated with ongoing network fluctuations during the UP state [74]. The role of background activity was also emphasized in a study in anesthetized animals where the shape of evoked responses varied significantly from one trial to the next, being highest under medium levels of anesthesia, during which ongoing cortical activity exhibits rhythmic population bursting activity [42]. It has been shown that the beginning of the UP state is associated with increased excitatory currents [33] and is characterized by highly structured activity within a population of neurons [50]. The notion of a period of relative unresponsiveness corresponding to the UP state, usually associated with an occurrence of a spindle [58, 75, 77], is consistent with the proposal that sleep spindles might have protective function for sleep by suppressing the flow of sensory information from the thalamus [100]. Spontaneous oscillations during sleep are efficient in gating the information not only from the outside but also modulate powerfully the intracortical communications. It is plausible that the initial portion of the UP state is only marginally affected by external perturbations because during this time each and every neuron is either involved in the generation of the action potential, or experiences afterhyperpolarisation. It can be speculated that the efficiency of generating highly synchronous bursts of neuronal activity might be crucial to achieve the recovery function of intense sleep. Thus, superficial light sleep with fewer slow waves with low amplitude is not recuperative as has been shown by slow wave suppression experiments [3].

6. BEHAVIORAL AND COGNITIVE DEFICITS AFTER SLEEP DEPRIVATION: WHAT ARE THE UNDERLYING MECHANISMS?

Spontaneous and especially prolonged waking has profound effects not only on brain activity but also on cognitive functions. For example, sleep deprivation leads to attention lapses, mistakes in cognitive and memory tasks [41] and microsleeps, which can have dangerous consequences in tasks requiring alertness [13]. Surprisingly, neuronal underpinnings of behavioral deficits after sleep deprivation remain unknown. A few *in vitro* studies have found that neuronal excitability and several other electrophysiological properties of individual cortical neurons are affected by preceding sleep-wake history [48, 99]. In turn, *in vivo* recordings of cortical unit activity in freely-behaving rats revealed that neurons fire more and more synchronously after prolonged waking, and less so after a period of consolidated sleep [95]. Moreover, LFP slow waves and their cellular counterpart – the periods of generalized neuronal silence–occurred more synchronously across large distributed cortical territories in early intense sleep after sleep deprivation [93]. Such changes in cortical neuronal activity should inevitably affect cortical function, and specifically the interaction of the organism with the outside world, manifested, for example, in an altered responsiveness of cortical neurons to incoming stimuli. One possibility is that after prolonged waking the neocortex switches transiently to a "sleep-like mode". Indeed, during acute and chronic sleep deprivation slower EEG activity, including SWA (0.5–4 Hz) or low theta (5–7 Hz) activity, leaks into periods of behavioral waking, and it does so in a region-specific manner [31, 47, 96]. Consistently, when wake is prolonged beyond its physiological duration, brain metabolism in awake subjects tends to decrease [29], as is typical for sleep. The EEG and behavioral manifestations of tiredness seem to occur in a correlated manner, as, for example, caffeine decreased both the rate of buildup of theta EEG activity during sleep deprivation and subjective ratings of sleepiness [45]. It was found recently that after sleep deprivation, local populations of cortical neurons in awake rats start undergoing brief OFF periods similar to those occurring during NREM sleep [93]. Thus, even during behavioral wakefulness, local populations of neurons in the cortex may be "falling asleep", with potential negative consequences on performance. However, neither the mechanisms underlying such local and global wake-dependent changes in cortical neuronal activity, nor the neuronal mechanisms underlying behavioral and cognitive deficits after sleep deprivation have been elucidated.

It can be suggested that increased cortical bistability is the primary cause of behavioral and cognitive deficits incurred after sleep deprivation, as it seems to affect neuronal responsiveness. Specifically, the occurrence of OFF periods, encompassing local neuronal populations, should on one hand result in a disruption of short-range neuronal coordination, since, by definition, all or most local neurons during such an OFF period are simultaneously deactivated or inhibited [19, 69] and do not produce spikes [49]. On the other hand, it can facilitate long-range responsiveness, because while hyperpolarized, neurons seem to be more easily excitable [24], but the only remaining source of the input in this case are distant neurons, not engaged in the local OFF period. In physiological conditions, network activity and neuronal responsiveness are continuously modulated by the balance of excitation and inhibition [33], which is maintained in a broad dynamical range [63]. It can be hypothesized that after sleep deprivation the balance between excitation and inhibition is maintained, but the stimuli elicit stronger excitatory responses that in turn recruit stronger inhibition, leading to an occurrence of longer periods of generalized inactivity.

Bistability of cortical neurons would, in turn, efficiently gate incoming thalamic and intracortical inputs, leading not only to a disconnection from the environment, but also to a breakdown of intracortical communications. It has been shown that early EPSPs evoked by long-range inputs arising from supragranular levels are remarkably voltage-dependent [36]. Specifically, at resting membrane potential the EPSPs are too small and brief to lead to action potentials, but grow several hundred folds with membrane depolarization [36]. Such state-dependency implies that specific long-range connections between distant cortical areas may only be fully functional in alert waking state, when supragranular neurons across the neocortex are tonically depolarized [64]. Instead, after sleep deprivation, when neurons in the supragranular layers tend to go briefly in a hyperpolarized state and are not sufficiently depolarized, incoming stimuli would often fail to elicit a significantly large EPSP. This would prevent long-range horizontal propagation of cortical excitation, leading to a loss of cortical integration. In turn, the breakdown of large-scale integration could be the primary mechanism underlying impaired executive functions, which require long-

range synchronisation between cortical areas, as manifested, for example in action planning and decision making that involve a concerted involvement of the fronto-parietal circuit [5].

CONCLUSIONS

Mechanisms underlying the manifold consequences of sleep deprivation remain elusive: one possibility is that it results in a failure to maintain the global brain state, leading to a general breakdown of all or most brain functions (top-down). Alternatively, staying awake could first affect, selectively and independently, individual cortical neurons or specific local neuronal circuits as a direct result of specific waking activities, affecting their corresponding functions (bottom-up). In either case, the main effects of sleep deprivation would be a disrupted local and global cortical dynamics that would invariably precipitate the occurrence of behavioural and cognitive deficits. Elucidating the mechanisms leading to wake- and experience-dependent changes in cortical neuronal activity after sleep deprivation will bring invaluable insights into our understanding of the function of sleep. In turn, uncovering how such changes in cortical neuronal activity translate into well-known behavioural and cognitive deficits typical for sleep deprivation is not only crucial for basic neuroscience but also for sleep-related issues of public health and safety.

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