Sleep Locally, Act Globally

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Abstract

In most animals, sleep is considered a global brain and behavioral state. However, recent intracortical recordings have shown that aspects of non–rapid eye movement (NREM) sleep and wakefulness can occur simultaneously in different parts of the cortex in mammals, including humans. Paradoxically, however, NREM sleep still manifests as a global behavioral shutdown. In this review, the authors examine this paradox from an evolutionary perspective. On the basis of strategic modeling, they suggest that in animals with brains composed of heavily interconnected and functionally interdependent units, a global regulator of sleep maintains the behavioral shutdown that defines sleep and thereby ensures that local use-dependent functions are performed in a safe and efficient manner. This novel perspective has implications for understanding deficits in human cognitive performance resulting from sleep deprivation, sleep disorders such as sleepwalking, changes in consciousness that occur during sleep, and the function of sleep itself.

Keywords

evolution, function, homeostasis, sleepwalking, slow oscillation

Sleep is usually viewed as a global brain and behavioral state. A sleeping animal is inactive with closed eyes, largely unaware of its surroundings, and thereby rendered vulnerable to predation (Lima and Rattenborg 2007). Only with sufficient stimulation does a sleeping animal rapidly return to a wakeful state of environmental awareness. Exceptions occur among marine mammals (Lyamin and others 2008; Mukhametov and others 1977) and birds (Rattenborg and others 2000), which can sleep with one eye open, a behavior associated with an interhemispheric asymmetry in non–rapid eye movement (NREM) sleep intensity, or unihemispheric sleep. This form of local sleep allows such animals to keep an eye out for predators and conspecifics (Lyamin and others 2008; Rattenborg and others 1999) and, in marine mammals (Lyamin and others 2008), to swim and breathe while obtaining some sleep (Fig. 1). Recent intracortical recordings have revealed that aspects of NREM sleep and wakefulness also occur simultaneously in different parts of the cortex in terrestrial mammals, including humans (Nir and others 2011; Nobili and others 2011; Vyazovskiy and others 2011). Nonetheless, rather than resulting in a mixed sleep/wake behavioral state, NREM sleep still manifests as a global behavioral shutdown, the definition of sleep itself (Lima and Rattenborg 2007). In this respect, the paradox that defines rapid eye movement (REM) sleep—an activated brain in a behaviorally asleep animal—also exists locally during NREM sleep.

In this review, we attempt to explain this paradox by integrating the recent findings on local sleep within an evolutionary framework. In a recent strategic model, we suggested that in heavily interconnected brains with functionally interdependent neural components, wherein mixed wake/sleep states may result in maladaptive behavior, engaging in a global behavioral shutdown is often the safest or most efficient way to sleep (Lima and Rattenborg 2007). This model, however, did not account for the recent discovery of wake-like neuronal activity occurring locally in the cortex of behaviorally asleep animals. Herein, we suggest that by initiating and maintaining the behavioral shutdown, global mechanisms of sleep regulation in the hypothalamus ensure that homeostatically regulated local sleep processes in the cortex occur in the safest and most efficient manner possible, even when parts of the brain enter wake-like states.

Sleep in Mammals and Birds

Although sleep has been found in all animals thoroughly studied (Cirelli and Tononi 2008), only mammals and birds exhibit unequivocal NREM and REM sleep, a similarity that arose via convergent evolution (Rattenborg

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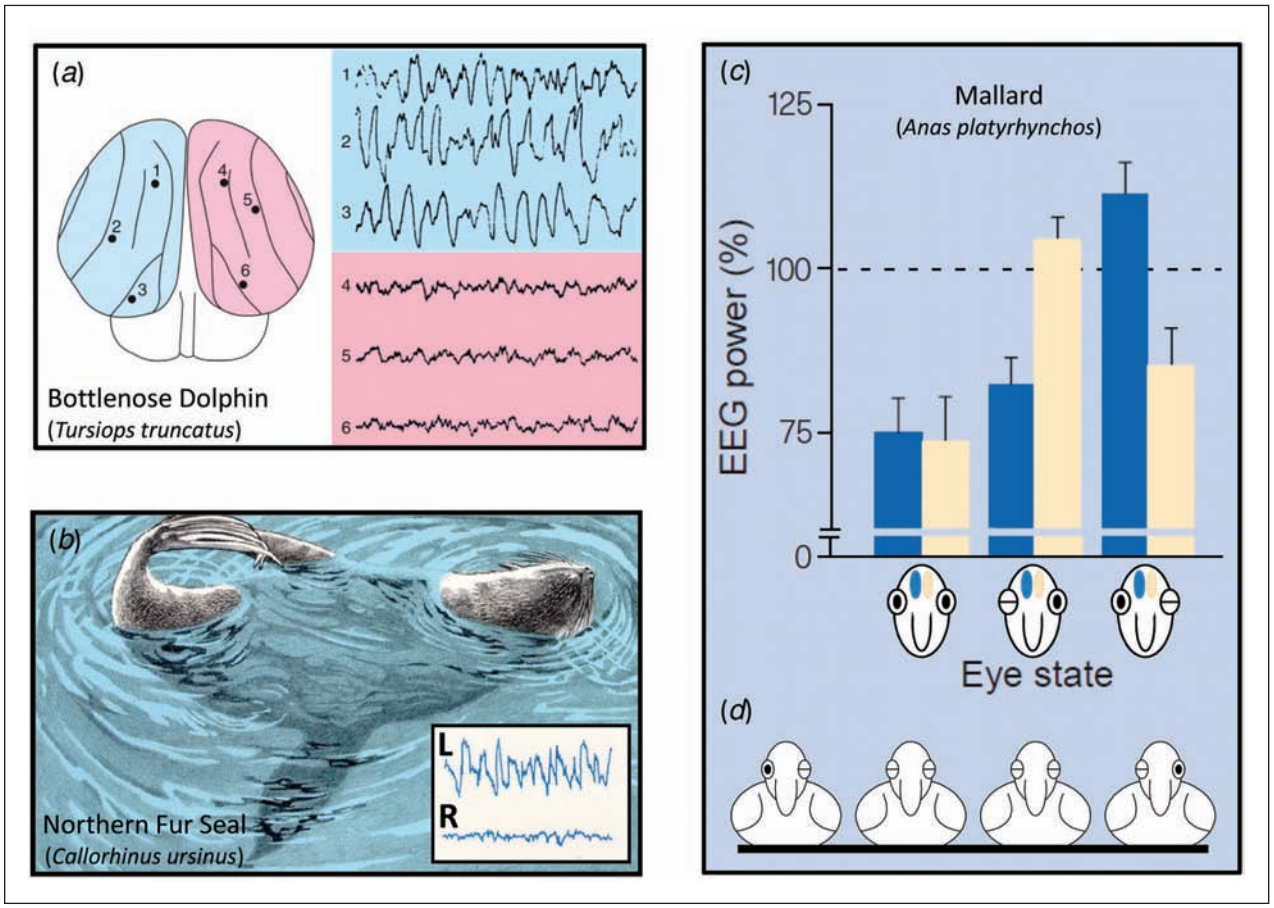

Figure 1. Unihemispheric and asymmetric non–rapid eye movement (NREM) sleep in marine mammals and birds. Unihemispheric NREM sleep is associated with electroencephalogram (EEG) activity characteristic of NREM sleep (high-amplitude, low-frequency waves) in one hemisphere and wakefulness (low-amplitude, high-frequency) in the other, whereas asymmetric NREM sleep is characterized by NREM sleep in one hemisphere and a state intermediate between unequivocal NREM sleep and wakefulness in the other. During both states, the eye projecting to the more awake hemisphere remains open monitoring the environment. (*a*) EEG recorded from the left (1–3) and right (4–6) brain hemisphere of a dolphin showing sleep (blue) in only the left hemisphere. (*b*) Fur seals engage in unihemispheric or asymmetric NREM sleep while floating on their side. The flipper opposite the more awake hemisphere paddles to keep the seal's nostrils above the surface. (*c*) Mallard ducks sleeping with one eye open show an interhemispheric asymmetry in low-frequency EEG power (1–6 Hz) during NREM sleep. Power in the left (sand) and right (blue) hemispheres is expressed as a percentage of that occurring during NREM sleep with both eyes closed. (*d*) Mallard ducks sleeping at the edge of a group spend more time sleeping with one eye open than those safely flanked by other birds and direct the open eye away from the other ducks, as if watching for approaching predators. Adapted from (*a*) Mukhametov and others (1977); (*b*) reprinted with permission of Grass-Telefactor, An Astro-Med, Inc. Product Group; and (*c*) Rattenborg and others (1999).

2007) (Fig. 2). Despite a pronounced difference in the organization of pallial neurons (i.e., laminar in the mammalian cortex and nuclear in the avian pallium) (Jarvis and others 2005; Fig. 2), mammals and birds share the hallmark of NREM sleep, the synchronized cortical (or pallial) slow oscillation (<1 Hz) of neuronal membrane potentials between a hyperpolarized down-state without action potentials and a depolarized up-state with action potentials (Reiner and others 2001; Steriade 2006). In mammals, the slow oscillation is an intrinsic property of the cortex that typically originates in frontal regions and propagates as a traveling wave in an anterior-posterior direction (Massimini and others 2004; Murphy and others 2009; Nir and others 2011; Ruiz-Mejias and others 2011; Volgushev and others 2006; Vyazovskiy , Faraguna and others 2009). Although the thalamus is not necessary for the genesis of cortical slow oscillations, thalamic input has been implicated in initiating NREM sleep (Magnin and others 2010) and further synchronizing the cortical slow oscillation (Crunelli and Hughes 2010).

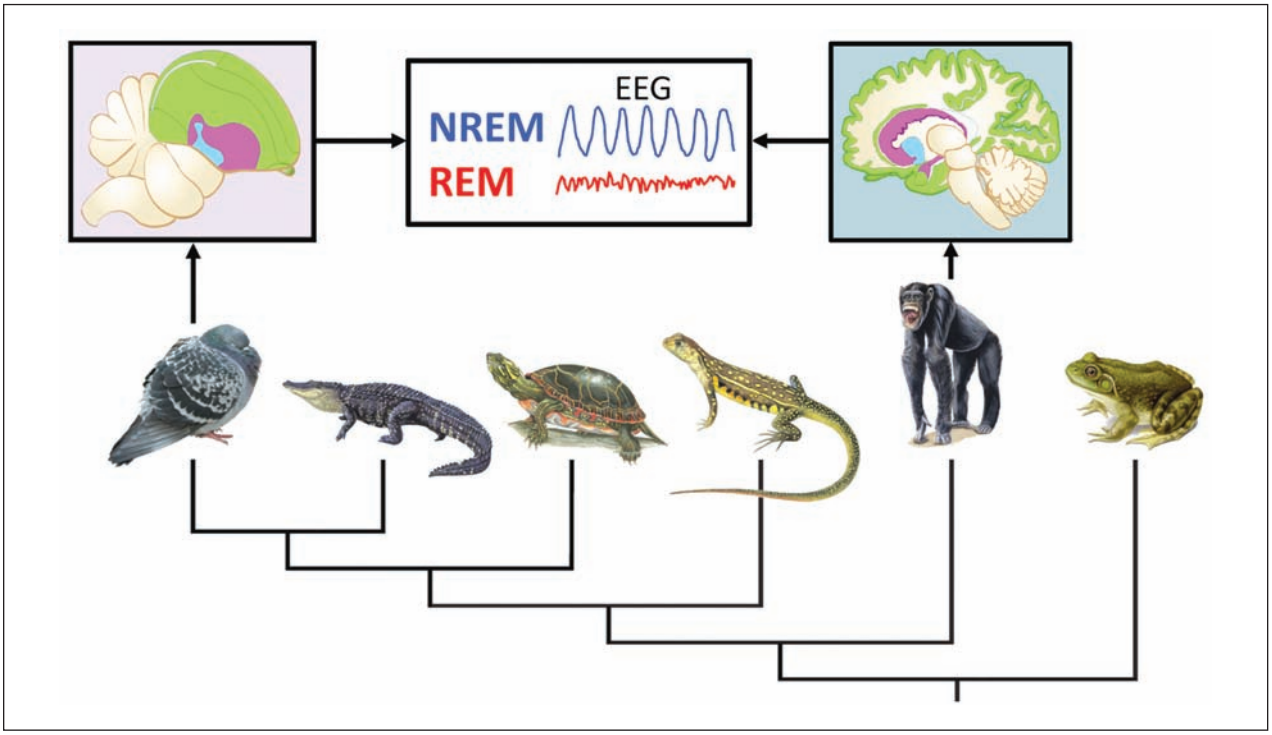

Figure 2. An evolutionary tree for tetrapods showing the convergent evolution of rapid eye movement (REM) and non-REM (NREM) sleep in mammals and birds. Although the other tetrapods sleep, their brains do not generate the electroencephalogram (EEG) activity that characterizes NREM or REM sleep in mammals and birds. This might be related to the fact that mammals and birds also independently evolved large, heavily interconnected brains capable of performing complex cognitive processes. The sagittal view of a bird and human brain shows that although the pallium (green) is enlarged in birds and mammals, unlike the laminar arrangement of pallial neurons in the mammalian cortex, pallial neurons in the avian forebrain are arranged in a largely nuclear manner. The striatum and pallidum are shown in lavender and light blue, respectively. Adapted from Jarvis and others (2005) and Rattenborg and others (2009).

Interactions between multiple cortical slow oscillations result in high electroencephalogram (EEG) slow-wave activity (SWA; 0.5- to 4.0-Hz power density) during NREM sleep (Esser and others 2007; Riedner and others 2007; Steriade 2006). Although the total time spent in NREM sleep appears to be determined by, as of yet, unknown factors (Davis and others 2011), SWA is the best predictor of prior sleep/wake history. Specifically, the amount of NREM sleep-related SWA increases and decreases as a function of prior time spent awake and asleep, respectively, in mammals (Tobler 2011) and birds (Rattenborg and others 2009). SWA and the underlying slow oscillation are thought to be involved in a homeostatically regulated process closely tied to the function of NREM sleep (Tononi and Cirelli 2006; Krueger and others 2008).

Local, Use-Dependent Sleep

A growing body of research has shown that NREM sleep is homeostatically regulated locally in the cortex in response to local waking brain use, as first formally predicted by Krueger and Obál (1993). Following the discovery of unihemispheric NREM sleep in dolphins (Mukhametov and others 1977), a subsequent unihemispheric sleep deprivation study suggested that NREM sleep is homeostatically regulated independently in each hemisphere (Oleksenko and others 1992; see also Lyamin and others 2008). However, given that unihemispheric NREM sleep is a whole-hemisphere phenomenon (Lyamin and others 2008), and each hemisphere includes a duplicate of all cortical and subcortical structures implicated in sleep regulation (Lapierre and others 2007), it was unclear from this study whether sleep is homeostatically regulated by subcortical regions within a hemisphere or local factors within the cortex (Krueger and others 2008). In addition, this study only measured time spent in NREM sleep for each hemisphere, rather than EEG SWA occurring during NREM sleep. The local, use-dependent homeostatic regulation of NREM sleep-related SWA in the cortex was established in a series of studies in humans (Huber and others 2004; Kattler and others

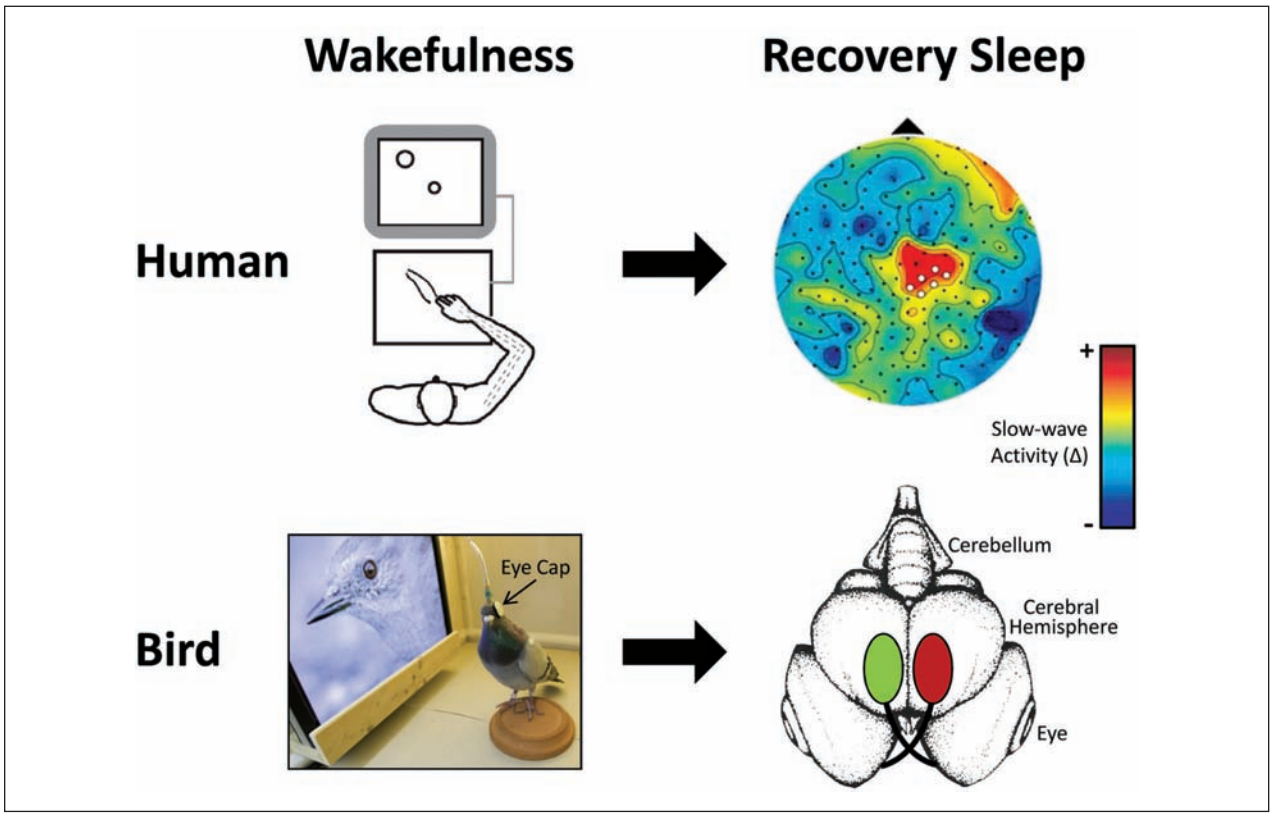

Figure 3. Local, use-dependent regulation of non–rapid eye movement (NREM) sleep in mammals and birds. (*a*) In humans, high-density electroencephalogram (EEG) recordings show a local increase in slow-wave activity (SWA)—a measure of sleep intensity—in the right parietal cortex during NREM sleep following performance of a visuomotor task. Colors depict local increases (dark red) and decreases (dark blue) in SWA from baseline NREM sleep. White spots show electrode sites that reached statistical significance. (*b*) In pigeons, watching David Attenborough's *The Life of Birds* (BBC) with only the right eye resulted in a local increase in EEG SWA in the left hyperpallium, a primary visual processing area. The change in SWA from baseline sleep is color coded as in the human brain above. Modified from Huber and others (2004), Landsness and others (2009), and Lesku and others (2011).

1994; Landsness and others 2009) and rats (Hanlon and others 2009; Vyazovskiy and others 2000; Vyazovskiy and others 2008) that induced a local increase in SWA in cortical regions by selectively activating those regions during prior wakefulness (Fig. 3). Similarly, reducing activation of a cortical region diminished subsequent SWA in that region (Huber and others 2006). In addition to the cortex, a recent study suggests that similar processes may also occur in the hippocampus (Moroni and others 2008). Collectively, these studies demonstrate that SWA is regulated locally within the mammalian cortex as a function of the level of local brain use during prior wakefulness, thereby suggesting that sleep serves a function for the cortex itself.

A recent study suggests that local, use-dependent regulation is also a feature of avian NREM sleep (Lesku and others 2011; Fig. 3). Although previous studies had shown that NREM sleep SWA is homeostatically regulated in birds (Rattenborg and others 2009), these studies did not establish that SWA increases in response to brain use per se. Given the independent evolution of NREM sleep and the marked differences in pallial cytoarchitecture between birds and mammals, it was possible that avian NREM sleep might be regulated only via subpallial mechanisms within a hemisphere. To determine whether SWA increases in response to local brain use, pigeons were kept entirely awake while watching David Attenborough's *The Life of Birds* with only one eye (Fig. 3). For each hemisphere, the EEG was recorded from the hyperpallium, a primary visual region receiving projections primarily from the contralateral eye (Ortega and others 2008), and the mesopallium, a nonvisual region implicated in forming high-order associations (Mehlhorn and others 2010). During subsequent recovery sleep with both eyes uncovered, SWA during NREM sleep showed a similar increase in the left and right mesopallia. In contrast

to the mesopallium, however, SWA increased only in the hyperpallium previously visually stimulated. Interestingly, despite being sleep deprived, the visually deprived hyperpallium did not show a change in SWA from baseline. Increased time spent awake and decreased visual input during sleep deprivation may have had opposing effects on recovery SWA (i.e., the former increasing and the latter decreasing SWA) that cancelled out one another under these conditions (Lesku and others 2011). These findings show that use-dependent factors within the avian pallium play a role in sleep regulation, as in the mammalian cortex. Importantly, the presence of similar findings in mammals and birds suggests that local regulation is a fundamental feature of NREM sleep and perhaps sleep in general.

The exact mechanisms and functions linked to the local, use-dependent regulation of NREM sleep are not yet well established. Mechanistically, substances produced during local activation of the cortex (e.g., adenosine, nitrous oxide, cytokines, and growth hormone–releasing hormone) are thought to accumulate during wakefulness and alter the firing properties of cortical neurons, resulting in greater SWA during NREM sleep (Bjorness and others 2009; Churchill and others 2008; Halassa and others 2009; Krueger and others 2008; Liao and others 2010; Yoshida and others 2004). Use-dependent increases in the strength and number of synapses may also cause local increases in SWA by increasing the synchrony of slow oscillations (Faraguna and others 2008; Hanlon and others 2009; Vyazovskiy and others 2008; Vyazovskiy, Olcese and others 2009). Current functional theories fall into two nonmutually exclusive categories: 1) NREM sleep replenishes neuronal resources depleted during waking use, or 2) NREM sleep modifies changes in synaptic connections resulting from waking use. Specifically, local sleep may restore levels of energy (Bennington and Heller 1995; Scharf and others 2008) or proteins (Mackiewicz and others 2007) depleted during wakefulness. Proposed synaptic changes occurring during local sleep include the consolidation of newly formed synapses through the reactivation of prior waking neuronal activity patterns (Diekelmann and Born 2010), the weakening (down-scaling) of synapses mediated by the slow oscillation (Tononi and Cirelli 2006), or the rescaling (up or down) of synapses (Krueger and others 2008). Although resolving the details of local sleep regulation is essential for our understanding of sleep, a critical examination of each theory is beyond the scope of this review (see reviews: Diekelmann and Born 2010; Krueger and others 2008; Tononi and Cirelli 2006). For our purposes herein, it is sufficient to say that NREM sleep is involved in locally regulated use-dependent processes that presumably support waking brain performance.

Local Wakefulness during Global Sleep

Although local sleep intensity is modulated by local brain use, the EEG-based studies discussed above suggest that NREM sleep is still a global brain phenomenon. Regions used more intensively may sleep more deeply, but this sleep occurs concurrently with sleep in the rest of the brain. In contrast to the EEG, which averages neural activity across large areas, recent intracortical local field potential (LFP) and multiunit activity (MUA) recordings in humans suggest that aspects of wakefulness may occur during NREM sleep. LFP and MUA recordings were obtained from multiple cortical regions in patients with epilepsy undergoing presurgical diagnostic testing (Nir and others 2011). During stable episodes of NREM sleep, the MUA recordings showed alternations between high neuronal firing and neuronal silence occurring in conjunction with slow waves in the LFPs. The alternation between such on- and off-states presumably is associated with the slow oscillation of neuronal membrane potentials between up- and down-states, as described in cats (Steriade 2006). Interestingly, alternations between on- and off-states could occur globally or locally, that is, in >50% or <50% of the recorded regions, respectively (see also Rector and others 2005). Thalamocortical spindles also occurred locally but were not associated with local oscillations between on- and off-states. Regardless of the time of night, local oscillations were more frequent than global oscillations. Frontal regions within and between hemispheres were more likely to oscillate together than posterior or temporal regions. Global oscillations were more frequent early in the night and occurred in conjunction with high-amplitude slow waves in the surface EEG. In contrast, local oscillations were only associated with slow waves in nearby LFP recordings. During late NREM sleep, much of the cortex remained in the on-state characteristic of wakefulness.

In a similar study, Nobili and colleagues also found that sleep and wake-like activity can occur simultaneously in the human brain (Nobili and others 2011). In this study, intracortical EEG recordings were obtained from the motor cortex (MC) and the dorsolateral prefrontal cortex (dlPFC) of patients with epilepsy. As in the previous study (Nir and others 2011), local activations were frequently observed and usually involved the MC showing a wake-like activation, whereas the dlPFC showed a pattern typical of NREM sleep (Fig. 4). Interestingly, slow frequencies in the dlPFC increased immediately before and during activations in the MC. The occurrence of local activations increased across the night and within individual phases of NREM sleep, reaching a maximum shortly before entry into REM sleep. Collectively, these two studies reveal a previously unknown capacity for the

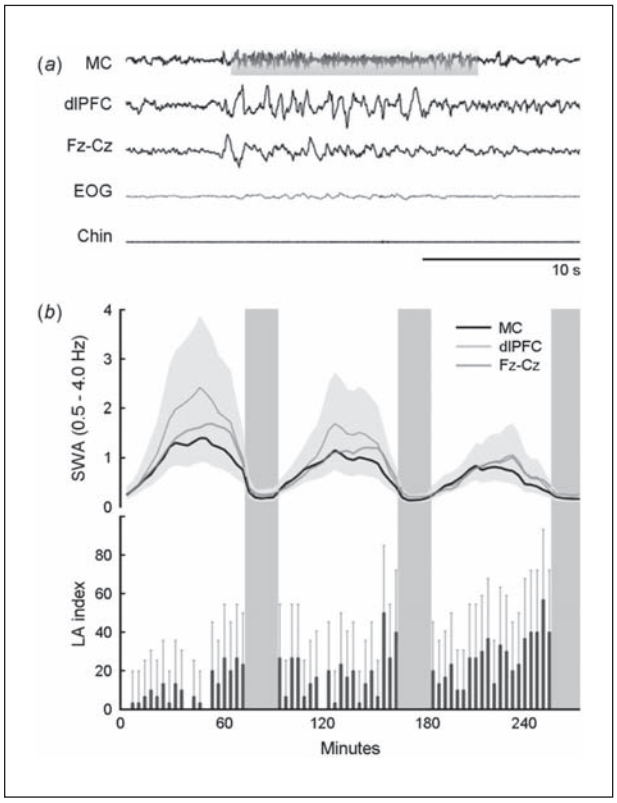

Figure 4. Local wakefulness in sleeping humans. (*a*) Simultaneous recording of intracortical electroencephalogram (EEG) from the motor cortex (MC) and dorsolateral prefrontal cortex (dlPFC), scalp EEG (Fz-Cz), electrooculogram (EOG), and electromyogram (chin) showing local activation of the MC (gray shading) during non–rapid eye movement (NREM) sleep. (*b*) Temporal relationship between (*top*) normalized slow-wave activity (gray area shows confidence interval) and (*bottom*) the index of local activations (LA/h of NREM sleep) in the MC (error bars show confidence intervals). Vertical gray bars indicate REM sleep. Adapted from Nobili and others (2011).

human brain to exhibit local wake-like activity during NREM sleep. Moreover, the recent discovery of similar local aspects of NREM sleep in rats suggests that the findings in humans with epilepsy reflect a normal and general feature of mammalian sleep (Vyazovskiy and others 2011).

Local Sleep during Global Wakefulness

In addition to wake-like activity occurring locally during NREM sleep, aspects of NREM sleep can also occur locally in awake animals. The first hint that this might be possible came from a report on neuronal activity in a monkey (*Macaca fascicularis*) performing a visual task (Pigarev and others 1997). As the monkey started to show behavioral signs of drowsiness (slow drifting eye movements), previously responsive neurons in visual area V4 reduced their firing rate, a pattern similar to that recorded during subsequent sleep. Although the drowsy monkey continued to perform the task, apparently via lower-level visual areas, performance was slightly reduced. This study suggested that some components of waking behavior can persist even when some brain regions appear to be falling asleep. In contrast to the monkey that was showing behavioral signs of drowsiness, Vyazovskiy and colleagues recently showed that sleep-related neuronal activity can also occur in clearly awake rats (Vyazovskiy and others 2011). LFP and MUA were recorded from the frontal motor cortex and the parietal cortex of freely moving rats during a relatively short (four-hour) period of sleep deprivation and subsequent recovery sleep. Although less frequent than during NREM sleep, global and local off-states occurred while the rats appeared behaviorally awake (i.e., immobile in an awake posture, eyes open, and responsive to stimuli) (Fig. 5). Importantly, off-states could even occur asynchronously between individual neurons within one particular brain region. Entry into global and local off-states, as well as the ratio of global/local off-states, increased across the sleep deprivation period (Fig. 5). This association with sleep debt lends evidence to the notion that such off-states are linked to homeostatically regulated sleep processes. Although the rats appeared globally awake during these events, performance on a motor task was impaired if an off-state occurred in the frontal motor cortex, but not the parietal cortex, 400 to 700 ms before performance of the task. Off-states occurring during wakefulness were associated with 2- to 6-Hz waves in the LFP recordings, a finding that may explain the increase in EEG theta power previously reported during sleep deprivation in rats (Vyazovskiy and Tobler 2005) and humans (Finelli and others 2000). Collectively, this suggests that local sleep may be at least one component of the cascade from full alertness to global sleep that contributes to deficits in human neurobehavioral performance following sleep deprivation (Van Dongen and others 2011; Walker and others 2011).

Why Go Global?

Vyazovskiy and colleagues raise the intriguing question of whether sleep-like off-states in awake animals reflect an adaptive or a maladaptive response to sleep loss (Vyazovskiy and others 2011). Local sleep could be adaptive if it allows some beneficial sleep-related processes to occur while the animal continues to engage in adaptive waking behaviors. However, others have suggested that being partially asleep may be unproductive or

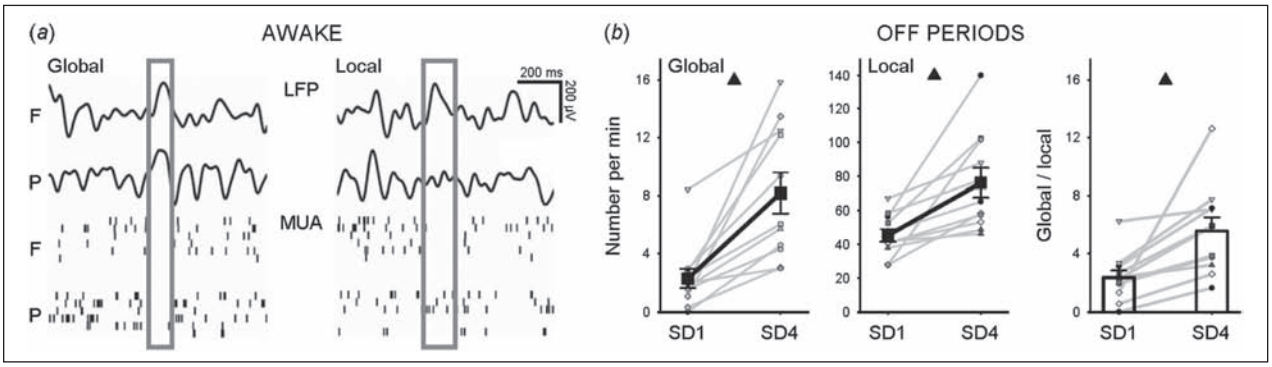

Figure 5. Local sleep in an awake mammal. (*a*) Local field potentials (LFPs) recorded from the frontal (F) and parietal (P) cortex of an awake rat and raster plots of corresponding multiunit activity (MUA). During wakefulness, LFPs show low-amplitude, high-frequency waves and irregular, tonic MUA. Patterns characteristic of sleep can appear in an otherwise awake animal, as indicated by an off-state in the MUA associated with a high-amplitude, slow LFP. Such sleep can occur globally (*left*) or locally (*right*). (*b*) Global and local off-states/slow waves (2–6 Hz) increase toward the end of sleep deprivation (SD4) relative to the beginning (SD1); global off-states show a greater increase than local off-states, presumably reflecting increased sleep need. Gray lines: individual rats; black lines: mean ± SE; triangles indicate a significant difference between conditions. Reprinted from Vyazovskiy and others (2011).

even dangerous (e.g., Krueger and others 2008; Saper and others 2010).

As shown using strategic evolutionary modeling, being partially awake may be dangerous only under specific circumstances (Lima and Rattenborg 2007). In this simple mathematical model, individual neuronal units (which could be interpreted as neurons, cortical columns, etc.) are able to sleep independently from one another, as recently shown in rats (Vyazovskiy and others 2011), and each unit is assumed to require a certain daily amount of time in a sleep state characterized by unresponsiveness to input. When sleep in individual units has no influence over the performance of other units, deficits in performance (e.g., predator detection) are only proportional to the number of neural units asleep at any given time (Fig. 6a). Interestingly, under these circumstances, it does not matter whether sleep is accomplished locally with only some units at a time or globally with all units at the same time; the net deficit across the day is the same. For example, in an animal with brain units that each need 12 hours of sleep per day, the net performance across the day is the same regardless of whether sleep occurs with all units at the same time for 12 hours or with only half of the units in each brain region (sensory, association, and motor) at any given time (Fig. 6b). This counterintuitive finding indicates that sleeping in a piecemeal manner per se is not detrimental.

However, piecemeal sleep is decidedly unfavorable when sleeping units impair the performance of waking units, as is likely the case in heavily interconnected brains with functionally interdependent units (Lima and Rattenborg 2007) (Fig. 6a,b). In this case, global sleep with a complete behavioral shutdown is usually the safest way to fulfill daily sleep requirements. Despite being a state of maximal vulnerability, engaging in global sleep for a shorter period of time is safer overall than sleeping in a piecemeal manner for a longer period of time in animals with brains composed of functionally interdependent units. Although necessarily simplistic, this model may thus explain why sleep is usually characterized by a global behavioral shutdown. From this perspective, the function of sleep, as defined by this fundamental behavioral feature of sleep, is to ensure that local, use-dependent sleep processes take place in the safest and most efficient manner possible.

Predictions stemming from this strategic model of local sleep remain largely untested. Direct evidence is lacking for the assumption that sleep in one brain region has an adverse effect on the performance of an awake region, but such effects seem likely. The model also predicts that animals that regularly engage in unihemispheric or interhemispherically asymmetric NREM sleep (Fig. 1) (Lyamin and others 2008; Rattenborg and others 2000) should show less functional interdependence between the hemispheres during (bihemispheric) wakefulness than animals that engage exclusively in bihemispheric NREM sleep (e.g., all terrestrial mammals examined). This prediction may hold for at least some components of the avian visual system. The visual hyperpallium of each hemisphere receives input primarily from the contralateral eye, and information encoded in a given hyperpallium is only accessible when the bird uses the contralateral eye (Ortega and others 2008). This functional independence during bihemispheric wakefulness, presumably

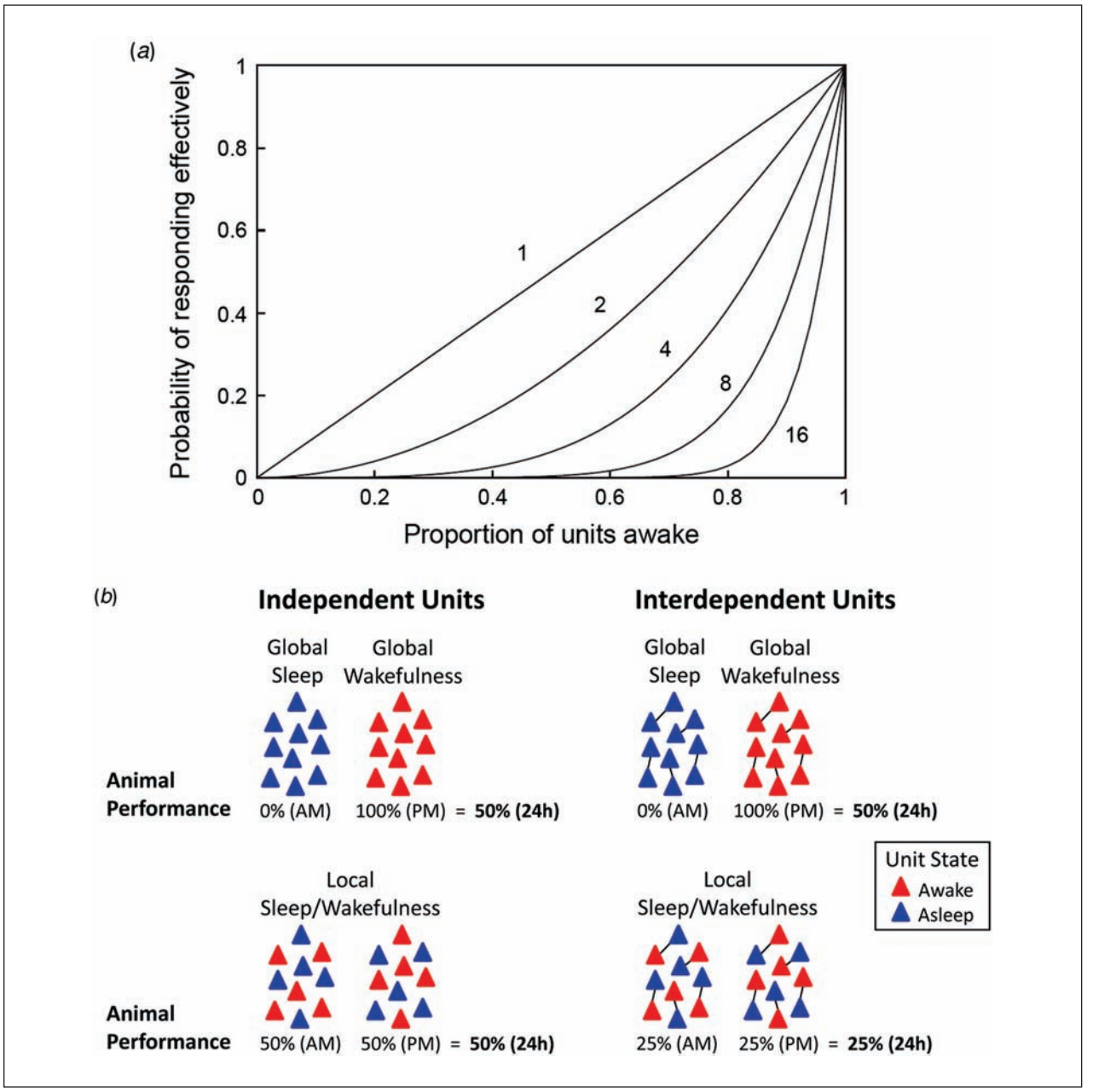

Figure 6. Strategic model of global ("shutdown") sleep. (*a*) The probability of responding effectively on a task (e.g., detecting and evading a predator) increases with the proportion of neural units that are awake. However, for a given proportion of neural units awake, performance declines as the functional interdependence of the brain units increases; interdependence of units is graphed from 1 (complete independence of units) to 16 (high interdependence). (*b*) Example of a theoretical brain composed of 10 neural units (triangles). In this brain, each unit requires 12 hours of sleep per day. Asleep (blue) and awake (red) units contribute 0% and 100%, respectively, to the animal's performance (the average of all units). When the units are functionally independent of one another (*left*, as in line 1 in part *a*), it does not matter whether sleep occurs globally with all units at a time for 12 hours or locally (e.g., with half of the units at a time); the average animal performance is 50% across the 24-hour period. However, global sleep is the best option when the neural units are functionally interdependent. For example (*right*), in a brain composed of interdependent units (indicated by the connecting line), wherein sleep in one unit decreases the performance of an awake unit by 50% (equivalent to line 2 in part *a*), engaging in global sleep results in 24-hour performance twice that resulting from sleeping with half of the units at a time. Thus, even though global sleep is a particularly dangerous and unproductive state, at least for achieving waking demands, it is the optimal form of sleep in brains composed of interdependent neural units. Adapted from Lima and Rattenborg (2007).

resulting from limited interhemispheric connections (Ortega and others 2008), likely enables birds to effectively monitor their environment when sleeping with one eye open (Rattenborg and others 1999). Although similar evidence for functional interhemispheric independence is lacking in dolphins, it has also been suggested that reduced interhemispheric connections contribute to the genesis of unihemispheric sleep (Lyamin and others 2008). Even if such connections are not the cause of unihemispheric sleep, by minimizing interhemispheric communication, they may allow unihemispheric sleep to occur in a safe and productive manner. Clearly, additional research is needed to determine the effects of local sleep on cognitive performance in animals capable of unihemispheric sleep, as well as those that engage exclusively in bihemispheric sleep.

Staying Global

Collectively, this strategic view of sleep and the recent discovery of local sleep-like activity in awake animals (Vyazovskiy and others 2011) and local wake-like activity in sleeping animals (Nir and others 2011; Nobili and others 2011) suggest that a global regulator of sleep may be needed to prevent maladaptive mixed sleep/wake behavioral states. Although individual neuronal units may be able to synchronize with one another on their own, resulting in global sleep (Roy and others 2008), a global regulator may expedite this process (Moruzzi 1966; Saper and others 2010) and maintain the behavioral shutdown when some regions enter a wake-like state independently from others, as shown during late sleep in humans (Nir and others 2011). For example, several lines of evidence suggest that during wakefulness, the prefrontal cortex (PFC) accumulates a greater need for sleep than other cortical regions and therefore sleeps more deeply early in the night (Achermann and others 2001; Finelli and others 2000; Finelli and others 2001; Harrison and others 2000; Maquet 2000; Massimini and others 2004; Nir and others 2011; Nobili and others 2011; Vyazovskiy and others 2000; Werth and others 1997). Consistent with these findings, frontal regions are less likely to enter wake-like states than posterior regions (Nir and others 2011; Nobili and others 2011). Given this regional gradient in sleep need and propensity to enter wake-like states, a global mechanism may be needed to ensure that local wake-like activity does not precipitate maladaptive mixed behavioral states.

Some pathological sleep states appear to reflect failures of global sleep regulation (Mahowald and others 2011). For instance, sleepwalking, a dangerous condition in humans that occurs when frontal regions remain asleep while other regions awaken (Bassetti and others 2000; Terzaghi and others 2009), may reflect the failure of such a mechanism. Interestingly, sleepwalking is more likely to occur early in the night and following sleep deprivation (Zadra and others 2008), possibly because the asymmetry between sleep need in the frontal and posterior regions is exacerbated under these conditions (Terzaghi and others 2009). In contrast to early in the night, late in the night, when sleep pressure in the PFC has dissipated and reached levels similar to those in the rest of the cortex (Finelli and others 2001; Werth and others 1997), arousals may be more likely to result in complete awakenings. Even at this time, when SWA has reached an asymptote, and prolonged local wake-like up-states are common, a global regulator may be needed to maintain the behavioral shutdown, especially if sleep occurring at this time serves an important function. Specifically, the behavioral shutdown may instantiate conditions required for proposed sleep functions linked to wake-like neuronal activity occurring during sleep (e.g., memory consolidation mediated by the reactivation of waking activity) (Diekelmann and Born 2010). Moreover, given that this neuronal activity may reflect prior waking experiences, rather than the immediate environment, the behavioral shutdown may prevent it from initiating maladaptive behavior (Krueger and others 2008).

For a global regulator of sleep to be beneficial, it must prevent brain regions that enter a wake-like state from disrupting the behavioral shutdown. Presumably, this requires that the relatively awake portions of the brain do not become overly responsive to the external environment. In this respect, a global regulator of sleep might exert its influence over the cortex by altering its processing characteristics. The increase in reports of dreams when awakened from NREM sleep occurring late in the night when compared with early in the night may provide some insight into this process (Nir and Tononi 2010). During early NREM sleep in humans, waves of slow oscillation on- and off-states propagate across the cortex (Massimini and others 2004). Although on-states may be associated with more wake-like processing (Destexhe and others 2007; Massimini and others 2003; Rector and others 2005; Rector and others 2009), they do not induce bursts of consciousness with changing qualities characteristic of the cortical regions experiencing the on-state at any given point in time. Indeed, when awakened from deep NREM sleep, people often fail to report any thoughts running through their mind. Increased cortical inhibition, or the resulting slow oscillations, may interfere with the ability of the cortex to integrate information across brain regions (i.e., effective connectivity), thereby accounting for the lack of thought at this time (Massimini and others 2005; Esser and others 2009; Massimini and others 2010; Nir and Tononi 2010). During late NREM sleep, however, slow oscillations diminish as sleep pressure wanes, wake-like on-states become longer (Vyazovskiy, Olcese

and others 2009), and reports of dreams increase and become more like the vivid dreams arising from REM sleep (Nir and Tononi 2010) when virtually the entire cortex remains in the on-state. Importantly, late NREM and REM sleep dreams do not simply reflect a gradually increasing awareness of the environment, as one might expect with more neurons staying in an awake-like on-state and the lower arousal thresholds associated with lower SWA at this time (Neckelmann and Ursin 1993). Instead, dreams remain focused on internally generated topics unrelated to the immediate environment. Thus, despite engaging in wake-like neuronal activity and associated dreams, the global behavioral shutdown that defines sleep is maintained, presumably through mechanisms that cause this fundamental difference in consciousness between sleep and wakefulness.

Global Enforcement

The search for brain regions involved in the global regulation of sleep has a long history. Despite extensive research, no single regulator of global sleep has been identified. Although brain lesions may cause temporary reductions in sleep, sleep is usually restored over time. This finding is consistent with the notion that sleep can be an emergent property of neuronal groups (Krueger and Obál 1993), as suggested by the local, use-dependent regulation of NREM sleep-related SWA. However, this does not necessarily indicate that sleep is not normally under the influence of global regulators. Indeed, lacking global regulation, the sleep that recurs following such lesions may be more local and likely to intrude into wakefulness. Furthermore, the persistence of sleep following brain lesions may simply indicate that there is redundancy in the global regulatory system, rather than the complete absence of global sleep regulation.

In this section, we describe many of the brain regions implicated in the global regulation of sleep (Saper and others 2010). While recognizing that the global regulation of sleep/wake states is likely mediated by distributed networks of reciprocally related elements (Hassani and others 2010), we pay particular attention to the preoptic area of the hypothalamus because it has been implicated in the alteration in consciousness that may maintain the behavioral shutdown during sleep. Several lines of evidence indicate that neurons in the ventrolateral preoptic area (VLPO) and median preoptic nucleus (MnPN) of the preoptic area of the hypothalamus are involved in the global regulation of sleep (Komarova and others 2008; Saper and others 2010; Szymusiak and others 1998). Neurons in the preoptic area are active during NREM and REM sleep and increase their activity during intense recovery NREM sleep following sleep deprivation (Szymusiak and others 1998). Only neurons in the MnPN increase their activity during sleep deprivation, suggesting that the MnPN is involved in the homeostatic sleep drive, whereas VLPO neurons are involved in maintaining sleep via input from the MnPN (Gvilia and others 2006). Although their role in promoting and maintaining sleep has been confirmed with lesion studies (Lu and others 2000), the exact mechanisms through which preoptic neurons measure sleep need remain unclear (Szymusiak 2010). Somnogenic factors produced during wakefulness in response to neural activity (e.g., nitrous oxide, adenosine, interleukin 1β, tumor necrosis factor–α, prostaglandin D_2) (Halassa and others 2009; Krueger and others 2008) may accumulate in the subarachnoid cerebrospinal fluid (CSF) and indirectly activate sleep-active neurons in the preoptic area (Morairty and others 2004; Scammel and others 1998; Scammel and others 2001; Szymusiak 2010). In addition to the role played by the VLPO in initiating and maintaining sleep, inhibition of the basal forebrain by the accumulation of adenosine may also facilitate sleep directly by reducing cholinergic transmission in the thalamus and cortex (Kalinchuk and others 2011; Strecker and others 2000). Finally, GABAergic NREM sleep-active neurons in the lateral hypothalamus (Hassani and others 2010), basal forebrain (Hassani and others 2009), and/or cortex (Kilduff and others 2011) may also be involved in the homeostatic regulation of global sleep. The exact manner in which these brain regions interact to establish global sleep remains unresolved.

The VLPO, in particular, may contribute to the behavioral shutdown through altering consciousness (John and others 2004). Preoptic area neurons provide inhibitory input to most components of the ascending arousal system, including the raphe system, locus coeruleus, periaqueductal gray matter, parabrachial nucleus, lateral hypothalamus, and the tuberomammillary nucleus (TMN) (Sherin and others 1998). Of these, the histaminergic TMN appears to play a prominent role in maintaining waking consciousness. In dogs with cataplexy, a disorder characterized by the intrusion of REM sleep-related muscle atonia into wakefulness, histamine, which is usually low during REM and NREM sleep, remains at the high levels characteristic of wakefulness, whereas the levels of other neuromodulators are at levels typical of REM sleep (John and others 2004). Given that humans, and presumably dogs, are fully aware of their surroundings during cataplexy, high levels of histamine are apparently needed to incorporate sensory stimuli into conscious experience (John and others 2004; Nir and Tononi 2010), that is, the difference between waking and sleeping consciousness. Consistent with these findings is the observation that TMN neurons—the source of histaminergic input to the entire cortex and subcortical regions involved in arousal (Lin and others 1996)—show the most wake-selective firing patterns identified in the brain (Takahashi and others 2006), and

knockout mice lacking histamine show persistent behavioral and EEG signs of sleepiness (Parmentier and others 2002). Given the direct inhibitory connections to the TMN from the VLPO (Sherin and others 1998), VLPO neurons active during NREM and REM sleep may thus inhibit histamine release in the cortex, alter consciousness, and thereby maintain the behavioral shutdown that defines sleep, even when parts of the brain exhibit wake-like activity (Nir and Tononi 2010). If this hypothesis is correct, then the increase in sleepiness observed in knockout mice lacking histamine (Parmentier and others 2002) should arise from more sleep-like neuronal activity occurring locally in the cortex during wakefulness.

Global Awareness

Even though parts of the brain may be in a wake-like state during late sleep, the transition from being asleep to being awake is marked by a rapid shift in focus to the outside world. As with falling asleep rapidly, awakening rapidly may avoid maladaptive mixed states (Saper and others 2010). In the absence of an external alarm clock, what determines that it is time to awaken? Declining sleep factors in the CSF impinging on the preoptic area may provide homeostatic feedback that leads to reduced activity in the MnPN and VLPO and thereby the release of wake-promoting histamine from the TMN. Homeostatic processes in the basal forebrain (Kalinchuk and others 2011) and indirect circadian input from the suprachiasmatic nucleus to the VLPO may also play a role (Aston-Jones and others 2001; Saper and others 2010). Finally, the PFC itself may be involved in awakening the rest of the brain. In addition to receiving input from all components of the arousal system, the PFC also projects to the basal forebrain, hypothalamus (including the VLPO), and the brainstem arousal systems (Aston-Jones and others 2005). Indeed, a recent imaging study showed that even during NREM sleep, the PFC may communicate with brainstem arousal systems (Dang-Vu and others 2008). Given the PFC's reciprocal connections with arousal systems and the rest of the cortex, as well as its executive role in waking brain functions, including directing attention and decision making (Tomita and others 1999), the PFC is strategically positioned to awaken the entire brain. Along these lines, albeit in the opposite direction, it has been suggested that the increase in slow frequencies in the dlPFC occurring during local activations in the MC in humans (Fig. 4) may reflect an "attempt" by the dlPFC to maintain global sleep (Nobili and others 2011). If such speculation is correct, then the PFC may also be involved in orchestrating global awakenings. Finally, as the cortical region with perhaps the greatest need for sleep (see above), it also makes sense for the PFC to play an executive role in this process. Homeostatic processes in the PFC itself may thus contribute to the timing of the final awakening (Kalinchuk and others 2011; Van Dort and others 2009).

Summary

The recent discoveries related to local sleep suggest that both local and global factors play complementary roles in the regulation of sleep. The local regulation of sleep allows sleep to be tailored to the specific use-dependent needs of cortical regions. However, the resulting regional differences in the intensity of sleep and propensity to awaken may also be problematic. Although allowing brain regions to awaken independently from one another might seemingly result in an adaptive increase in awareness of the environment, it may also lead to maladaptive behaviors in animals with brains composed of functionally interdependent components. Consequently, a global regulator of sleep, such as the hypothalamic preoptic area, may be needed to initiate and maintain the behavioral shutdown that defines sleep. This would minimize entry into maladaptive mixed states and prevent regions that enter wake-like states from disturbing sleep in other regions. In this respect, the function of the behavioral shutdown that defines sleep is to ensure that local, use-dependent functions are performed in a safe and efficient manner.

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