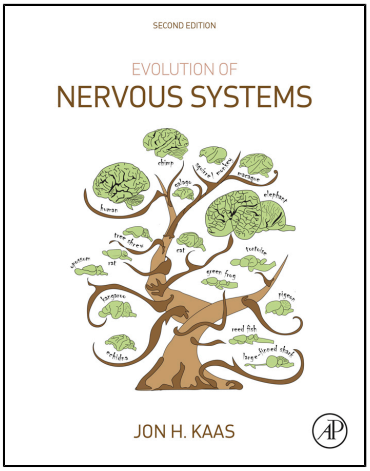




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# 3.28 Decomposing the Evolution of Sleep: Comparative and Developmental Approaches

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**Abstract**

Sleep is ubiquitous throughout the animal kingdom. Nonetheless, we still do not have a firm grasp on its functions. Whatever its functions, we should expect them to vary in accord with the diverse morphologies, physiologies, ecologies, and life histories of different species and taxonomic groups. Moreover, one apparently universal feature of sleep—documented in flies and worms, rats, and humans—is that it predominates early in development. Accordingly, both developmental and comparative approaches—and combined developmental comparative approaches whenever possible—are likely to prove vital for revealing the origins and functions of sleep.

## 3.28.1 Sleep Is a Complex Behavioral State

The waking state is filled with diverse and complex behaviors that evolved to promote survival and reproduction, including walking and running, eating and drinking, fighting and fleeing, mating and parenting, reading and talking. Whereas humans tend to experience their waking periods as single, protracted episodes that last 16 or more hours each day, many mammals and birds typically experience wakefulness in numerous and substantially smaller bouts. Interspersed between these bouts of wakefulness is sleep, which we now know to be as diverse and complex as wakefulness, and exceedingly more mysterious.

First and foremost, sleep is a behavioral state. Indeed, all animals studied thus far exhibit behavioral signs of sleep. At particular times of the day or night, animals seek out and find (or build) suitable resting places and adopt species-typical sleeping postures. Among invertebrates, nematodes (*Caenorhabditis elegans*) exhibit a sleeplike state called lethargus (Raizen et al., 2008), as does a marine invertebrate, the cuttlefish (*Sepia officinalis*; Frank et al., 2012; Corner, 2013b). Flies (*Drosophila melanogaster*), which are the most extensively studied of all invertebrates, exhibit many of the defining behavioral features of mammalian sleep, including an increased arousal threshold and homeostatic regulation (Shaw et al., 2000). Among fish, the zebrafish (*Dario rerio*) also exhibits compelling behavioral evidence of sleep (Yokogawa et al., 2007). Investigators have even provided evidence of life span changes to sleep in flies and zebrafish that bear similarities to those in mammals, including high levels of sleep in early development and sleep fragmentation with aging (Sorribes et al., 2013; Koh et al., 2006; Shaw et al., 2000; Kayser et al., 2014). The steadily increasing interest in sleep in such "simple" animals revolves in large part around the relative ease with which sleep regulation and function can be investigated at the molecular level (Hendricks et al., 2000).

In mammals and birds, there are two primary sleep states: quiet sleep (QS, or slow-wave sleep, or non-REM sleep) and active sleep (AS, or REM sleep). During the descent into QS, limbs relax, eyelids close and eyes are still, and breathing slows. With the arrival of AS, skeletal muscle tone is actively suppressed. Interestingly, this muscle paralysis is briefly interrupted by jerky twitches of the limbs, digits, eyes, and other appendages (eg, whiskers, bill, tail). Although laypeople and scientists alike have traditionally viewed these twitches as remnants of dreams, the true story is more complicated (Blumberg and Plumeau, 2016; Blumberg et al., 2013).

The behavioral manifestations of sleep are mirrored by electrographic changes in muscle (electromyography, EMG) and cerebral cortical (electroencephalography; EEG) activity. Whereas the EMG captures the suppression of muscle tone and the phasic muscle twitches of AS, the EEG captures the slow "delta" waves (1–4 Hz) that characterize QS in adult mammals and birds as well as the activated wakelike cortical activity of AS. The presence of wakelike brain activity in an otherwise sleeping animal is the basis for also referring to AS as paradoxical sleep. A third electrographic measure, the electrooculogram (EOG), captures the stillness of the eyes



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during QS and the rapid eye movements (REMs) of AS. Conventionally, and especially in clinical settings, EMG, EEG, and EOG measures are used to fully disambiguate the states of wakefulness, QS, and AS in adult mammals, especially humans. However, when investigations turn to infant mammals, nonmammalian vertebrates (eg, birds, reptiles), or invertebrates (eg, flies), conventional measures and criteria must be adjusted or abandoned.

The mysteries of sleep reside at both the mechanistic and functional levels. At the level of mechanism, neuroscientists have made great strides in revealing the neural structures that produce the various component features of QS and AS and how their destruction leads to sleep pathologies, such as REM sleep behavior disorder (eg, Luppi et al., 2011; Peever et al., 2014). Nonetheless, relatively little is known about how the dynamic interactions among these neural structures yield the temporal structure of sleep–wake states and the transitions among them. Nor do we know enough about how sleep is regulated homeostatically after periods of restriction or deprivation. Satisfactory resolution of these mechanistic mysteries will require a broader sampling across ages and species.

The biggest mystery of sleep concerns its functions: perhaps no other aspect of vertebrate life is so prominent and yet so poorly understood. We know why we are awake because we know why we eat and drink, why we fight, and why we mate. The obvious functional value of wake-related behaviors makes clear the functional value of wakefulness itself. So why do we sleep? By analogy with wake, we should not be seeking the functional value of a single process, but rather a suite of processes that are best performed during sleep. Nor should we necessarily expect those processes to be universal across all animals; on the contrary, the diverse morphologies, physiologies, ecologies, and life histories of different species should have no less an impact on an animal's sleep than on its waking life. Moreover, even if sleep, when it first evolved, initially served only one functional purpose, over time numerous other functions could have *accreted* into periods of sleep, resulting in a state of functional mosaicism that varies across different species and taxonomic groups. Accordingly, comparative approaches are vital for testing theories about the mechanisms and functions—and evolution—of sleep.

### 3.28.2 Sleep–Wake Cyclicity and Energy Allocation

The conflation of "sleep" with "rest" naturally led investigators to consider sleep a period of energy conservation (Berger and Phillips, 1995). The energy conservation theory, which for decades has been among the most seemingly plausible and highly cited theories of sleep, simply posits that sleep reduces across-the-board energy demands. As one basis of support for this theory, it was suggested that the high metabolic demands of endothermy (ie, internal heat production) in mammals and birds, in comparison with the lower metabolic demands of ectothermic fish and reptiles, drove the evolution of sleep in those two vertebrate classes (Allison and Van Twyver, 1970b); the suspension of thermoregulatory processes (eg, sweating, panting, shivering) during AS is also consistent with this view (Parmeggiani, 1987; Graf et al., 1987). In its simplest rendition, however, the energy conservation theory of sleep has not been strongly supported by empirical evidence. Specifically, the energy savings during sleep (in relation to wake) can be meager (Jung et al., 2011); moreover, during AS, the highly activated brain is indicative of more, not less, metabolic expenditure. Such negative evidence caused the energy conservation theory to fall into disfavor.

A more nuanced and biologically realistic account of the energetics of sleep was recently proposed (Schmidt, 2014). Instead of thinking about energy use increasing and decreasing *en bloc*, this new theory focuses on the state-dependent *allocation* of energy to specific processes that are best performed at different times (**Fig. 1**). For his theory, Schmidt adopts a life history approach that emphasizes the individual's energetic needs for growth, bodily maintenance and repair, and reproduction. He argues that these needs fluctuate across age and time of day, as well as across AS, QS, and wakefulness. Accordingly, in contrast to the earlier energy conservation theory in which the savings were achieved through a passive decrease in energy use, Schmidt envisions "a highly active and dynamic process in which certain biological processes, such as thermoregulatory effort and much of the cellular machinery needed for vigilance [ie, wakefulness], are *reduced*, while energy for other functions, such as macromolecule biosynthesis and memory consolidation, are *increased*. Although the net energy savings of sleep appears modest when superficially compared to wakefulness, it is the optimization of energy distribution over the 24-h period that allows for relative stability of energy utilization across behavioral states" (p. 131).

One advantage of Schmidt's energy allocation theory is that it provides a framework for understanding how sleep–wake cycling fits within the broader species diversity of rest–activity phenotypes. Specifically, sleep–wake cycling resides on a continuum of energy allocation strategies. At one end of the continuum, some mammalian species can face such extreme energy demands—often associated with reduced food availability—that the maintenance of a high body temperature becomes too costly. In response, these species adopt the energy-saving solution of allowing body temperature to fall each day (shallow or daily torpor) or for longer periods of time (deep torpor or hibernation). In either case, the decreases in body temperature are so substantial that sleep, as defined electrographically, and many other biological processes (including those at the cellular level) are not possible. Thus, torpor is not a deeper stage of sleep, but rather a distinct life history strategy with its own costs and benefits.

At the other end of the continuum, there are moments and periods in animals' lives when sleep is sacrificed for wakefulness to promote survival or reproductive success. For example, during the intensively competitive mating season in pectoral sandpipers (*Calidris melanotos*), males substantially reduce their time asleep over 3 weeks without apparent behavioral costs; importantly, the males that slept the least over this period were the most successful in producing offspring (Lesku et al., 2012). Similarly, despite being able to sleep in flight, great frigatebirds (*Fregata minor*) forgo large amounts of sleep when flying nonstop for up to 10 days (Rattenborg et al., 2016). As many birds make nonstop flights lasting days, weeks, or months, an ability to perform adaptively with limited sleep may be common among birds (Rattenborg, 2006) and perhaps other animals that face ecological demands that

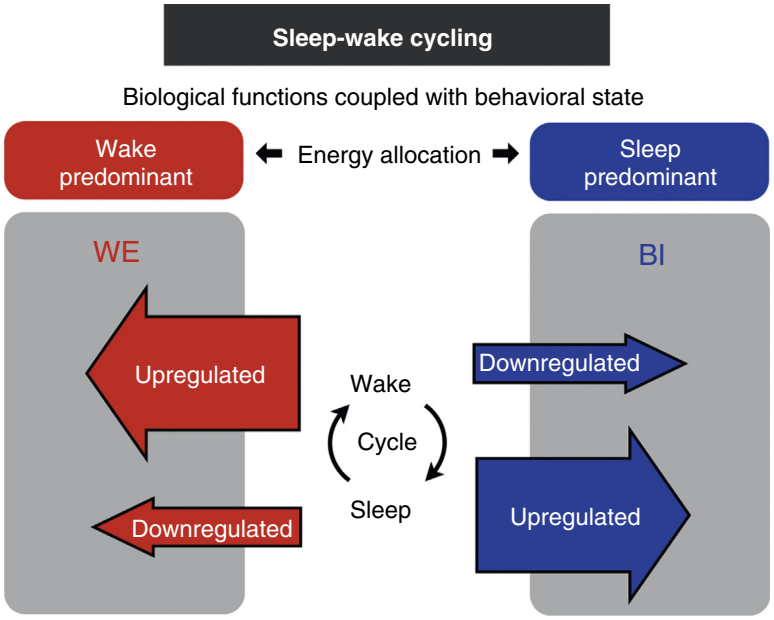


**Figure 1** A schematic depiction of Schmidt's energy allocation model as applied to sleep–wake cycling. According to this model, energy is allocated preferentially to wake to support such activities as foraging and reproduction, and allocated preferentially to sleep to support such activities as growth and repair. *WE*, waking effort; *BI*, biological investment. Reprinted with permission from Schmidt, M.H., 2014. The energy allocation function of sleep: a unifying theory of sleep, torpor, and continuous wakefulness. Neurosci. Biobehav. Rev. 47, 122–153, Copyright 2014, Elsevier Ltd.

require prolonged wakefulness in the wild (Siegel, 2009). Importantly, by demonstrating that reduced performance is not an evolutionarily inescapable outcome of sleep loss—a result that comports with Schmidt's energy allocation model (see Section 3.28.2)—these field-based studies on birds contribute to our theorizing about sleep's functions.

To account for torpor and prolonged wakefulness, the energy allocation theory posits that the functions that are normally accomplished during sleep are somehow accomplished in other ways and at other times. To test the theory, it will be important to determine if and how such reallocation of sleep-related processes occurs. Regardless, one clear benefit of the energy allocation theory is that it has reintroduced the concept of animal energetics to the field of sleep in a biologically grounded way and, by doing so, has opened new avenues for understanding the functions and phenotypic diversity of sleep.

### 3.28.3 What, if Anything, Is Special About Primate Sleep?

As with all mammalian orders, primates exhibit substantial variability across a variety of sleep dimensions. For example, three species have been identified as having the largest daily sleep quotas of 13–17 h each day: owl monkeys (*Aotus trivirgatus*), cotton top tamarins (*Saguinus oedipus*), and mouse lemurs (*Microcebus myoxinus*; Nunn et al., 2010). At the other end of the spectrum are those primates, including humans (Ohayon et al., 2004), that sleep fewer than 10 h each day. Hidden within these daily sleep quotas are additional dimensions of variability, such as the proportion of the total sleep time comprising AS or QS. For example, whereas the grivet (*Chlorocebus aethiops*), an Old World monkey, spends only 6% of its total sleep time in AS, humans spend 23% of their time in that state, the highest percentage among all primates for which such data exist (Samson and Nunn, 2015). Thus, among primates, humans are outliers in that they sleep relatively little but devote a relatively high proportion of sleep to AS.

Perhaps the most distinctive feature of primate sleep concerns *how* sleep is accumulated. In mammals, the apparently ancestral pattern is to accumulate sleep in many short bouts across the day and night (Capellini et al., 2008); such *polyphasic* sleep may reflect, especially in small-bodied mammals, the need to feed often to meet increased energy demands associated with high relative metabolic rates. In contrast, primates as a group evolved a strong tendency toward *monophasic* sleep, such that at least 50% of the daily sleep quota is concentrated in a single bout. This is true of humans, but also of the overwhelming majority of primate species studied thus far. This tendency toward monophasic sleep in primates could reflect increased sleep efficiency—that is, less time wasted transitioning into and out of sleep—and could be one of the many benefits of larger body size (Capellini et al., 2008).

The tendency toward monophasic sleep in humans and other anthropoid primates must be contrasted with recent arguments concerning the derived character of monophasic sleep in our species. Specifically, based on analyses of historical documents, it has been argued that a pattern of strictly monophasic sleep in humans is a recent response to changes in the availability of light at night. Prior to the Industrial Revolution, the argument goes, humans exhibited a "second sleep" in the middle of the nighttime period, thus contradicting the characterization of humans as strictly monophasic (Ekirch, 2006).

As compelling as this historical argument may be, a recent study of sleep in three hunter-gatherer societies in Africa and South America argues against the "second sleep" hypothesis (Yetish et al., 2015). Using activity monitors to measure sleep–wake patterns, individuals in these three societies slept from 5.7 to 7.1 h each day in one consolidated nighttime period (Fig. 2). Because the range of sleep durations is within the range of durations recorded in humans from industrial societies, these findings suggest that industrialization has not substantially altered human sleep habits, at least with regard to total sleep time. Further, the data suggest that the bimodal pattern of sleep, recently identified from the historical record in preindustrialized European societies, was a more recent response to life at higher latitudes and longer winter nights.

Mammals and birds sleep in a wide variety of species-typical positions and locations: curled up or sprawled out, standing upright or hanging upside down, in an underground burrow or out in the open, in a nest on the ground or in a tree, alone or in groups.

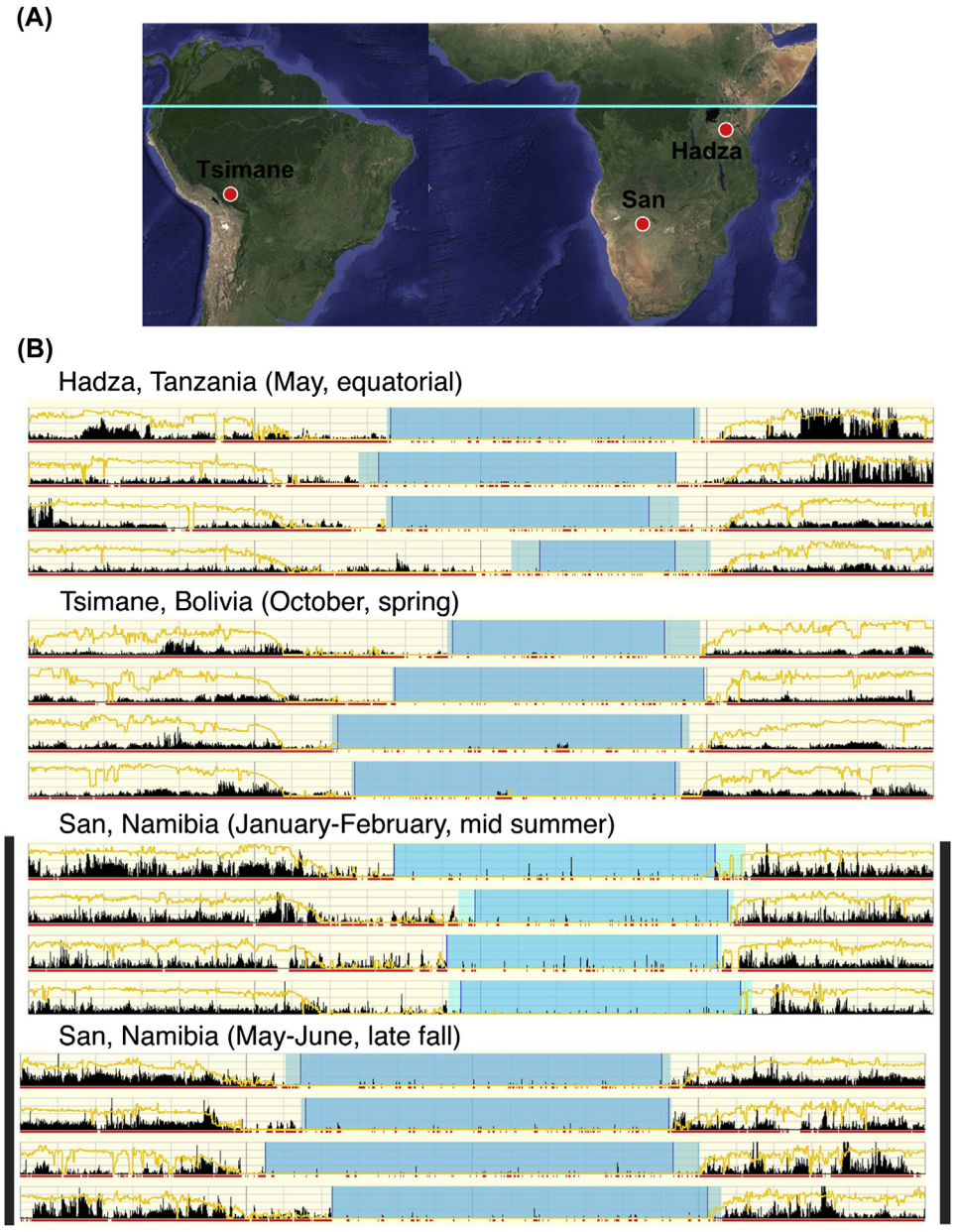


**Figure 2** Sleep duration measured with actigraphy in three preindustrial societies. (A) Location and names of the tribes. The *green line* shows the equator. (B) Actograms for one individual recorded across multiple days from each of the tribes. The San subject was also recorded across two seasons. Each plot shows the data from one 24-h day. The number of movements per minute is plotted in *black* and minutes with at least one movement are marked with the *red bar*. Changes in light levels (log plot) are in *yellow*. Times shaded in *light* and *dark blue* show periods of rest and sleep, respectively. Reprinted with permission from Yetish, G., et al., 2015. Natural sleep and its seasonal variations in three pre-industrial societies. Curr. Biol. 25 (21), 2862–2868, Copyright 2015, Elsevier Ltd.

Depending on the ecology and life history of the species, protected sleep sites serve to isolate the sleeper from arousing stimulation, conspecific competitors, predators, parasites and biting insects, and thermal challenges, as well as protect offspring when they are most fragile and vulnerable (Samson and Nunn, 2015; Kappeler, 1998).

In primates, four distinct types of sleep sites have been identified: fixed-point nests, tree branches, sleeping platforms in trees, and sleeping beds on the ground (**Fig. 3**; Samson and Nunn, 2015). A fixed-point nest can be a hole in a tree or a collection of leaves that offers protection and comfort to the smallest primates, such as galagos (genus *Galago*). The earliest primates would have likely used fixed-point nests until evolutionary increases in body size precluded their use. The next step, then, was to use tree branches for sleep, a transition that may also have coincided with the switch from nocturnality to diurnality and associated changes in group-living habits. Although gibbons and other lesser apes continue to sleep on tree branches, the great apes build sleeping platforms in trees that provide better support for their larger bodies. Because of the increased stability provided by these platforms, they may provide the opportunity for better sleep, thereby enhancing sleep-dependent cognitive functions in these highly encephalized primates; conversely, it may be that the enhanced cognitive powers of great apes enable them to engineer these platforms (for review, see Samson and Nunn, 2015).

Humans—the most encephalized species among the great apes—sleep on the ground and are the only primates to do so. The evolution of this trait appears to have arisen first in the upright-walking *Homo erectus*, perhaps owing to the unsuitability of bipedality for life (including sleep) in the trees. Regardless, sleep on the ground posed new threats (eg, predatory carnivores, disease-carrying insects) that would have had to be countered. For example, for ground-sleeping hominids, the use of fire—in addition to providing warmth—would have discouraged predation and insects while also fostering greater sociality. Sleeping on the ground may also have placed a premium on early humans to gain the greatest benefits from sleep in the shortest amount of time possible. Indeed, the "sleep intensity hypothesis" was proposed recently to account for why humans are so apparently unique in concentrating such a high percentage of AS into a relatively short period of consolidated sleep.

To sum up, comparisons among primate species are providing valuable insights into the factors that shaped the evolution of sleep within this relatively small taxonomic group. As discussed next, by broadening our vision further to include all mammals, as well as birds, reptiles, and invertebrates, the benefits of the comparative approach reveal themselves with even greater force.


**Figure 3** Types of sleep sites used by primates. (A) Fixed-point or cavity nests provide protection from predators and insulation from the weather during sleep (photo accredited to Manfred Eberle). (B) Tree branches provide protection from large predators, but are less stable than other sleep sites. (C) Some large-bodied great apes build stable sleeping platforms that provide thermal insulation and protection from biting insects and arboreal predators (photo accredited to Kathelijne Koops). (D) Terrestrial beds are used by massive apes (male chimpanzees and gorillas) and humans (photo of Hadza hunter accredited to Mathiew Paley). From Samson, D.R., Nunn, C.L., 2015. Sleep intensity and the evolution of human cognition. Evol. Anthropol. 24 (6), 225–237, Copyright 2015, courtesy of David Samson.

### 3.28.4 Lessons From Comparative Studies of Sleep

The study of sleep in animals can be viewed from several perspectives. The *model-based approach* aims to gain insight into sleep in humans by performing experiments on animals, such as laboratory rodents. More recently, the discovery of several similarities between sleep in flies and mammals has established flies as a powerful model for investigating the mechanisms and functions of sleep. In addition to this model-based approach, research on flies provides an example of a *comparative-based approach*, as studies in such "simple" animals may reveal the initial or core reason for the evolution of sleep (Hendricks et al., 2000). Consequently, both model- and comparative-based approaches, as applied in this context, usually focus on the similarities, rather than the differences across species. However, in our opinion, this focus undermines the full power of the traditional comparative approach, which aims to gain a more comprehensive understanding of biological phenomena by giving equal emphasis to similarities and differences across taxonomic groups.

In the case of sleep, a more balanced approach may be particularly important because once sleep evolved it likely took on additional functions, as several biological processes may be performed more effectively during sleep than wakefulness (as discussed in Section 3.28.2; Schmidt, 2014). A focus on differences can also reveal how shared functions can be performed via different mechanisms, or even call into question the necessity of certain mechanisms identified from studies that focus on only one taxonomic group. For example, in mammals, sleep-related brain rhythms are implicated in processing information acquired during wakefulness. However, flies perform similar processes during sleep, but they do so in the absence of mammal-like brain rhythms. Embracing and ultimately reconciling this difference will undoubtedly refine our understanding of the functions of mammalian brain rhythms. Consequently, an equal emphasis on the similarities *and* differences in sleep across taxonomic groups may provide insights into sleep that are obscured when we rely exclusively on a narrow model-based approach.

In the following section, we highlight both the similarities and differences between sleep across different taxonomic groups to further illustrate how a comparative approach can inform our understanding of mammalian sleep. We discuss QS and then AS. The section on QS first reviews the role that mammalian brain rhythms are thought to play in processing information, and then discusses how some, but not all, of these rhythms are unique to mammals. The section on AS addresses various aspects of this state and its evolution.

#### 3.28.4.1 Quiet Sleep

Although all animals exhibit a quiet sleep state, when we look at the "behavior" of the brain during sleep, marked differences are found across taxonomic groups. In some animals, such as flies, the brain becomes relatively quiescent during sleep, whereas in other animals the brain remains active during sleep but the pattern of brain activity (including the rhythms) is different. In many animals, sleep is itself composed of two states, each characterized, in part, by different patterns of brain activity, including different brain rhythms.

Deciphering the potential function of brain rhythms has been the subject of extensive research (Buzsáki, 2006). Although the number of studies linking sleep-related rhythms to memory processing in mammals continues to grow, several fundamental questions remain. Do mammalian rhythms play a causal role in processing memories or do they simply covary with other cellular processes responsible for processing memories? Is the frequency of a rhythm critically important or can rhythms of different frequencies perform the same function in different taxonomic groups (Voirin et al., 2014; Ramon et al., 2012)? Do all sleep rhythms have a function or are some rhythms epiphenomena that merely reflect the structure of the specific neuroanatomical circuits that underlie the rhythms? Although some of these questions are starting to be examined, others remain largely unexplored.

To establish a basis for comparing brain rhythms and the potential functional implications of differences across species, we first outline the roles that sleep-related brain rhythms are proposed to play in processing information in the mammalian brain. One prominent hypothesis, the synaptic homeostasis hypothesis, proposes that sleep improves performance by weeding out weak synapses and preserving recently used strong synapses (Tononi and Cirelli, 2003, 2014). In contrast, the memory reactivation hypothesis proposes that information acquired during wakefulness is reactivated, or "replayed," during sleep, resulting in the strengthening or addition of synapses, thereby improving postsleep performance (Dudai et al., 2015). Interestingly, despite their differences, both theories invoke the participation of QS-related slow oscillations of neuronal membrane potentials between hyperpolarized "down-states" with neuronal quiescence and depolarized "up-states" with action potentials (Steriade, 2006). According to the synaptic homeostasis hypothesis, the slow oscillation reduces synaptic strength by inducing long-term depression. In contrast, the memory reactivation hypothesis suggests that replay during the up-state of the slow oscillation leads to the strengthening of synapses via long-term potentiation.

Although the memory reactivation hypothesis might apply to various types of memory (Dudai et al., 2015), it is usually framed within the context of the standard model of hippocampal memory consolidation. According to this model, during wakefulness, information from high-order cortical association areas within the neocortex is funneled into the hippocampus. In the hippocampus, information is rapidly encoded into an integrated episodic memory of an event. Over time, however, recall of an event becomes less reliant on the hippocampus. According to the "active system consolidation model," the process of gradually "transferring" the memory from the hippocampus to the neocortex is mediated by the slow oscillation and its influence over other rhythms during sleep (**Fig. 4**; Dudai et al., 2015; Staresina et al., 2015). Specifically, during QS, the slow oscillation coordinates the timing of thalamocortical spindles (intermittent 12–15 Hz oscillations) and hippocampal sharp-wave ripples (SWRs) such that they cooccur during the up-state of the slow oscillation (Steriade, 2006). SWRs are highly synchronous bursts of activity during which neuronal

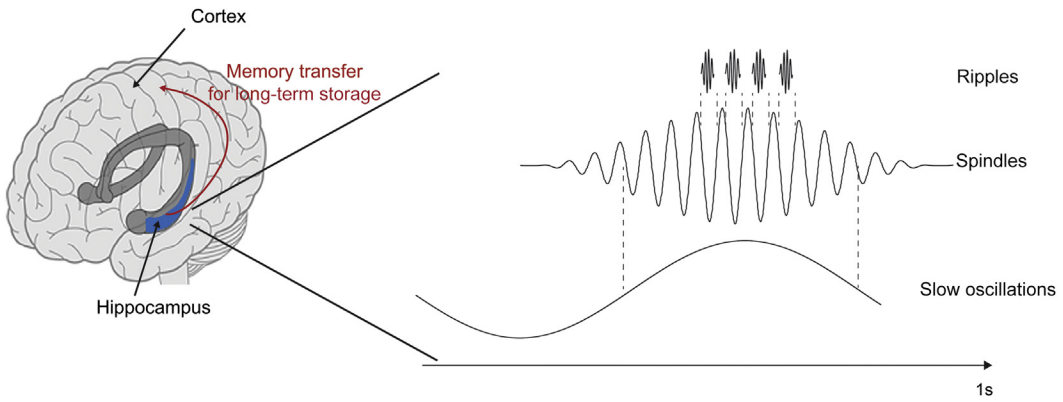


**Figure 4** Sleep-related brain rhythms implicated in transferring hippocampal memories to the neocortex for long-term storage and integration with preexisting memories. Neocortical slow oscillations influence the timing of hippocampal sharp-wave ripples (SWRs; only the ripple component is shown) and thalamocortical spindles such that they cooccur during the up-state of the slow oscillation. During SWRs, neuronal sequences activated during wakefulness are reactivated in the hippocampus and neocortex during quiet sleep. Spindles are thought to create conditions conducive to strengthening the reactivated synapses in the neocortex. The repeated reactivation of hippocampal memories is thought to lead to their transfer to the neocortex. Courtesy of Mathilde Bonnefond.

sequences activated during wakefulness are replayed in the hippocampus and in the neocortex in a coordinated manner in conjunction with spindles (Buzsáki, 2015). Cortical spindles are thought to create conditions conducive to the strengthening of the cortical memory being replayed. Over time, this process may lead to the transfer of memories from the hippocampus to the neocortex where they are integrated with preexisting memories for long-term storage.

Birds provide a particularly informative comparison with mammals, as many, but importantly not all aspects of their sleep are similar to mammals. To fully appreciate the functional implications of this comparison, we first need to compare the brains of mammals and birds. Despite being a type of dinosaur, birds are in many respects more similar to mammals than their closer living reptilian relatives. Notably, both mammals and birds are endotherms with large brains for their body size. In addition to having large brains, neuron density in birds is equal to or even higher than in primates (Olkowicz et al., 2016). Perhaps as a result, some birds are capable of performing complex cognitive tasks that are comparable to those exhibited by primates (Güntürkün and Bugnyar, 2016). For example, New Caledonian crows (*Corvus moneduloides*) can manufacture and use tools (Clayton and Emery, 2015). Interestingly, despite these similarities between mammals and birds, there are major differences in hippocampal neuroanatomy and neurophysiology (Rattenborg and Martinez-Gonzalez, 2013; Rattenborg et al., 2011). In contrast to the mammalian hippocampus which is reciprocally connected with high-order associative regions receiving input from most of the neocortex, the avian hippocampus only receives olfactory and visual input; most high-order associative brain regions do not connect to the hippocampus (Shanahan et al., 2013). Moreover, there is no solid evidence for the mammalian-like transfer of information out of the avian hippocampus. Collectively, this indicates that the scope of information reaching the hippocampus and the manner in which it is subsequently processed differs between mammals and birds.

As a result, it is perhaps not surprising that there are both similarities and differences in sleep between mammals and birds (Rattenborg et al., 2011). Like mammals, birds exhibit two types of sleep, QS and AS. As in mammals, avian QS is distinguished from wakefulness by high-amplitude slow waves in the EEG, and AS is characterized by a wakelike activated EEG pattern. As in mammals, slow waves propagate through the avian brain as traveling waves (Beckers et al., 2014). However, neither thalamocortical spindles (which are closely associated with slow waves in mammals) nor SWRs have been detected in birds during QS. These neurophysiological differences lend support to the proposed role that spindles and SWRs play in processing hippocampal memories in mammals; that is, birds might have no need for these rhythms because their hippocampus does not perform the memory transfer functions associated with them in mammals. Importantly, however, this bird/mammal comparison also suggests that slow waves serve a function unrelated to transferring hippocampal memories in both birds and mammals. In this respect, focusing on the differences between sleep in birds and mammals can help to sharpen our understanding of mammalian sleep.

What might be the general function of slow waves shared by birds and mammals? One clue rests in the regulation of slow waves in each group. In mammals, sleep deprivation is followed by an increase in the intensity (number and amplitude) of slow waves during subsequent recovery QS. The discovery of unihemispheric QS in some marine mammals (Lyamin et al., 2008) and birds (Rattenborg et al., 2000) led to the idea that the increase in slow waves following sleep deprivation reflects local use-dependent processes occurring in the neocortex (Krueger and Obal, 1993). Indeed, several studies have shown that the intensity of slow waves varies locally as a function of local waking brain use in mammals, including humans (Huber et al., 2004). As in mammals, slow waves increase following sleep deprivation in birds (Martinez-Gonzalez et al., 2008; Rattenborg et al., 2009). In addition, when parts of the avian brain are stimulated more than others during wakefulness, the previously stimulated parts show increased slow-wave intensity during recovery sleep (**Fig. 5**; Lesku et al., 2011). Consequently, unlike hippocampal memory transfer, the local, use-dependent homeostatic regulation of slow waves seems to be a fundamental aspect of QS shared by mammals and birds. Slow

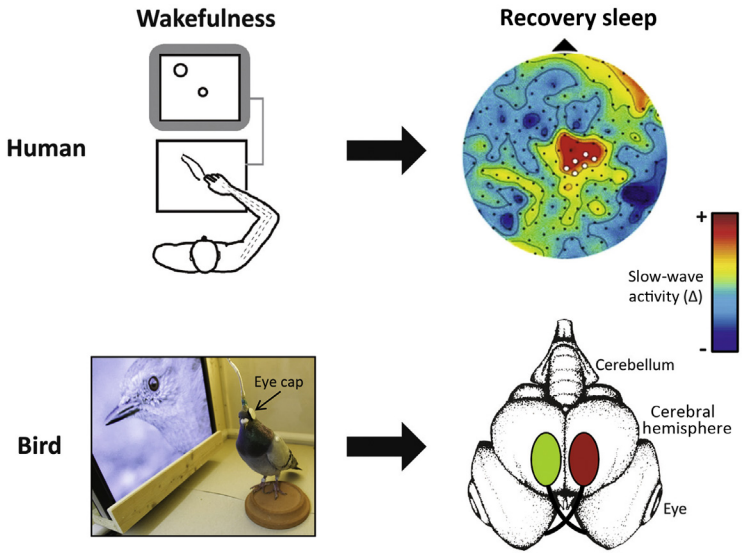


**Figure 5** Local, use-dependent regulation of electroencephalogram (EEG) slow-wave activity (SWA) in humans and pigeons during QS (quiet sleep or slow-wave sleep, SWS). In humans, high-density EEG recordings show a local increase in SWA—a measure of sleep intensity—in the right parietal neocortex during QS following performance of a visuomotor task. Colors depict local increases (*dark red*) and decreases (*dark blue*) in SWA from baseline QS. *White spots* show electrode sites that reached statistical significance. In pigeons, watching David Attenborough's *The Life of Birds* (BBC) with only the right eye while kept entirely awake resulted in a local increase in EEG SWA in the stimulated left hyperpallium (*red oval*), a primary visual processing area, but not the unstimulated right hyperpallium (*green oval*). The change in SWA from baseline sleep is color coded as in the human brain above. Reprinted with permission from Rattenborg, N.C., Lima, S.L., Lesku, J.A., 2012. Sleep locally, act globally. Neuroscientist 18 (5), 533–546, Copyright 2012, Sage Publications.

waves may be involved in processing information locally via memory reactivation (Chauvette et al., 2012) or synaptic homeostasis (Huber et al., 2004).

Despite the differences in the hippocampal system between mammals and birds, sleep has been implicated in processing other types of information in birds. Sleep plays a role in auditory discrimination in adult starlings (*Sturnus vulgaris*; Brawn et al., 2010), imprinting in young chickens (*Gallus domesticus*; Jackson et al., 2008), and song learning in young male zebra finches (*Taeniopygia guttata*; Brawn and Margoliash, 2015; Moorman et al., 2015). The research on finches is of particular interest because the effect sleep has on learning is difficult to interpret within existing models of sleep-dependent memory consolidation. During song learning, juvenile males attempt to reproduce the song of their father, a gradual process that spans months; interestingly, the quality of the song actually degrades during nightly sleep and improves with waking practice during the day (Deregnaucourt et al., 2005; Shank and Margoliash, 2009). Over a longer timescale, however, a more interesting pattern emerges: how well a male ultimately replicates its father's song is predicted by how much the song degraded across nightly sleep earlier in life. The mechanisms behind this unprecedented type of sleep-dependent memory processing remain unknown and do not readily fit within the framework of current models regarding sleep's role in memory processing. As such, song learning in zebra finches further underscores how comparative research can reveal aspects of sleep that challenge our current understanding.

As discussed earlier, the discovery of unihemispheric QS in marine mammals and birds likely motivated studies linking slow waves to local, use-dependent processes that occur in the human neocortex (Huber et al., 2004). A recent study provides an even more striking example of how comparative findings can directly inform our understanding of the sleeping human brain (Tamaki et al., 2016). Mallard ducks (*Anas platyrhynchos*) and fur seals are able to switch from sleeping with both hemispheres simultaneously (like terrestrial mammals) to sleeping with one hemisphere at a time in response to changing ecological demands. When compared to ducks sleeping safely inside a group, those sleeping exposed at the edge of the group spend more time sleeping unihemispherically; these individuals direct the open eye away from the other birds, as if watching for approaching predators (Rattenborg et al., 1999). Similarly, northern fur seals (*Calorhinus ursinus*) switch from sleeping bihemispherically on land to sleeping unihemispherically in the water (Lyamin et al., 2008). Although this sleep pattern facilitates keeping the nostrils above the surface, it may also serve an antipredator function, as seals keep the open eye facing down into the water, perhaps to detect approaching sharks.

Based on these findings in ducks and fur seals, Tamaki et al. (2016) asked whether a similar process might explain why people sleep poorly on their first night in a new environment. Remarkably, they found that the left hemisphere showed lower slow-wave (or delta) activity during QS and was more responsive to auditory stimuli than the right hemisphere only on the first night. In addition, individuals with greater interhemispheric asymmetry took longer to fall asleep. Collectively, this suggests that like ducks and fur seals, humans have some capacity to regulate the depth of sleep locally in the neocortex in response to potentially threatening ecological circumstances. This capacity to increase environmental awareness during sleep may have been particularly important

when human ancestors transitioned from sleeping in the trees to sleeping on the ground (see Section 3.28.3). If replicated, this study further demonstrates how even the most unusual comparative research can be surprisingly relevant to understanding sleep in humans.

Given the similarities between slow waves occurring during mammalian and avian QS, a natural question is whether this feature of QS evolved independently in each lineage or was inherited from a common ancestor. Clues to resolving this question can be gleaned from examining sleep in nonavian reptiles, amphibians, and fish. Although sleep in fish and amphibians remains poorly studied, especially at the electrophysiological level, several reptilian species have been examined. Unfortunately, unlike mammals and birds in which virtually all studies find fundamentally similar sleep states, the results from reptiles and other vertebrates are far more diverse and difficult to interpret (Hartse, 1994; Libourel and Herrel, 2016; Rattenborg, 2007). Although some of this diversity may reflect genuine interspecific differences, in some cases markedly dissimilar results were reported by different labs studying the same species. This suggests that the characterization of sleep in these groups is more sensitive to the recording method (eg, differences in electrode placement) and environment (eg, the physiological state of ectothermic reptiles depends on ambient temperature) than in mammals and birds. Lacking a resolution of these issues, the following scenario for the evolution of QS-related slow waves should be viewed as tentative.

Despite discrepancies, several studies report consistent findings in nonavian reptiles. Notably, QS behavior is often accompanied by intermittent high-voltage sharp waves emerging from a low-amplitude background EEG. Hartse (1994) suggested that these high-voltage sharp waves are homologous to hippocampal SWRs as they (1) have a similar morphology and duration, (2) increase following sleep deprivation, and (3) respond similarly to pharmacological manipulations. However, unlike mammalian SWRs that seem to be restricted to the hippocampus, high-voltage sharp waves occur within the reptilian hippocampus as well as in other forebrain areas (Rattenborg et al., 2011; Shein-Idelson et al., 2016). Moreover, SWRs have not been found in the avian hippocampus. Consequently, high-voltage sharp waves might be related to a more widespread neural phenomenon found in birds and mammals. For example, high-voltage sharp waves may reflect short and infrequently occurring up-states homologous to the longer-duration and more frequent up-states that characterize the EEG slow waves in mammals and birds. If this scenario is correct, it suggests that mammals and birds independently evolved increased investments in time spent in up-states. As up-states have been implicated in memory reactivation, these sleep-related functions may be more pronounced in mammals and birds, perhaps contributing to the maintenance of their large brains and complex cognitive abilities. Interestingly, according to this scenario, increased investment in up-states was necessarily accompanied by decreased investment in down-states. Although the function of down-states remains unclear, the absence of neuronal activity suggests that they might allow for cellular rest (Vyazovskiy and Harris, 2013). If correct, this suggests that an interesting trade-off exists between memory reactivation and cellular rest, with mammals and birds investing more in the former at the expense of the later. In this regard, focusing on both the similarities and differences among sleep in reptiles, birds, and mammals can inform our theories about the evolution and functions of sleep in mammals.

Although insects are distantly related to the vertebrates discussed earlier, important similarities and differences exist that also inform our understanding of mammalian sleep. Kaiser and Steiner-Kaiser (1983) were the first to describe changes in central nervous system activity during sleep in an invertebrate. In bees, the spontaneous firing rate and responsiveness of optomotor interneurons were reduced at night when the animals exhibited sleep behavior. Subsequently, local field potential recordings from the brain in flies showed a reduction in power across a broad range of frequencies, with no frequencies showing an increase during sleep (van Alphen et al., 2013). Similarly, calcium imaging showed that neurons become quiet during sleep in flies (Bushey et al., 2015). Although the decreased neuronal activity observed in flies is similar to the quiet down-states of the slow oscillations observed in mammals and birds during QS, it is unknown whether they reflect homologous states.

Despite the apparent absence of sleep-specific brain rhythms in flies, sleep is implicated in processes attributed to brain rhythms in mammalian sleep. Notably, sleep is associated with synaptic homeostasis (Donlea et al., 2009; Gilestro et al., 2009) and memory consolidation (Donlea et al., 2011) in flies. Assuming that brain rhythms have not simply evaded detection in flies, these findings indicate that similar functions can be performed in flies without those rhythms that characterize mammalian sleep. Although these findings raise questions about the necessity of brain rhythms for such processes, it is also possible that our understanding of sleep's role in processing information is not yet refined enough to distinguish between processes performed by rhythms and those that occur independent of rhythms. In this regard, efforts to understand this difference should lead to novel insights into the mechanisms and functions of mammalian sleep that might otherwise be missed if we focus only on similarities between taxa.

#### 3.28.4.2 Active Sleep

Only mammals and birds exhibit unequivocal AS. Like QS, the nature of AS varies across mammalian and avian species. Whereas some commonly recognized components of this state are missing in some species, others are found in virtually all mammals and birds examined thus far, even under circumstances where such components seem to interfere with ecological demands. As such, it may be that the shared aspects of AS are more likely to be linked with the fundamental function of this state. Finally, studies in basal mammals and birds provide a tentative picture of the evolutionary steps leading to AS in other mammals and birds.

The architecture of avian REM sleep bears many similarities to mammalian REM sleep, as well as some potentially informative differences. As in mammals, in several (but not all) avian species, the number and duration of REM sleep episodes increases across the night (Martinez-Gonzalez et al., 2008; Szymczak et al., 1996; Low et al., 2008). Moreover, the amount of REM sleep increases following short- and long-term sleep deprivation in pigeons (Tobler and Borbély, 1988; Martinez-Gonzalez et al., 2008; Newman et al., 2009). Despite these similarities, and in contrast to mammals, individual episodes of REM sleep tend to be very short in birds,

usually not lasting more than 10 s. [The short duration of REM sleep episodes does not appear to be an adaptation to protect them from falling out of trees, as REM sleep episodes are also short in large birds that sleep on land (Dewasmes et al., 1985).] In contrast with adult mammals, but similar to infant mammals (see Section 3.28.5.1), birds may have hundreds of REM sleep episodes within a day; this indicates that either the functions of REM sleep in birds can be completed within relatively short time intervals or entry into REM sleep is simply needed to initiate processes (ie, gene expression) that have carryover effects extending beyond each individual episode of REM sleep.

Features of AS commonly identified in laboratory mammals include EEG activation, a hippocampal theta rhythm, muscle atonia, twitching (of which REMs are one expression; Seelke et al., 2005; Chase and Morales, 1983), and reduced thermoregulatory responses. However, in some species, several components commonly used to identify AS in laboratory mammals are missing or are associated with QS instead. For example, although AS is associated with EEG activation in birds, a mammal-like hippocampal theta rhythm has not been observed in birds during AS (Rattenborg et al., 2011). This difference may reflect differences in hippocampal neuroanatomy and function, as discussed previously for QS-related SWRs. Consequently, the hippocampal theta rhythm is not a necessary component of AS (in the sense that the absence of this single AS component carries with it the absence of all other components). As another example, moles and owls exhibit AS, but lack REMs. In moles, this is related to their regressed visual system (Allison and Van Twyver, 1970a), whereas in owls it is due to their eyes being largely fixed in the eye sockets (Berger and Walker, 1972). Consequently, REMs are also not a necessary component of this state (although the broader category of twitching may be; see below). Finally, like other mammals, armadillos (*Chaetophractus villosus*) exhibit penile erections during sleep, but these erections occur during QS rather than AS. Apparently, this difference is related to the fact that erections in armadillos are mediated via muscular mechanisms, rather than vascular mechanisms as in other mammals (Affanni et al., 2001). This last example shows that erections are not specifically tied to REM sleep. Collectively, these examples illustrate how comparing AS across species can help identify those components that are fundamental—mechanistically or functionally—to this state.

From a strictly behavioral standpoint, AS is defined by the presence of twitching in an otherwise sleeping animal. In addition to mammals and birds, twitching has been reported in adult green iguanas (Ayala-Guerrero and Mexicano, 2008), honeybees (Klein et al., 2008), and cephalopods (Frank et al., 2012; Corner, 2013b), although more work is needed to confirm these observations and relate the movements to putative AS. Reduced muscle tone also appears to be a necessary component of AS. For example, many ungulates can stand during QS, but they only engage in AS while lying down (Ruckebusch, 1972; Tobler and Schwierin, 1996), a posture that increases the time it takes to respond to a predatory threat. The fact that they still engage in AS despite this risk indicates that AS serves an important function that requires reduced muscle tone. Otherwise, AS should have disappeared entirely in ungulates, or been modified such that the other features of the state (cortical activation) could occur without atonia.

Marine mammals also experience reduced muscle tone during AS, even though it can interfere with breathing (Lyamin et al., 2008). Although sea otters (*Enhydra lutris*) can float on their back with their head held out of the water during QS, during apparent AS their muscles relax and the head falls below the surface (**Fig. 6**; Lyamin and Oleksenko, 2000). Similarly, fur seals (family

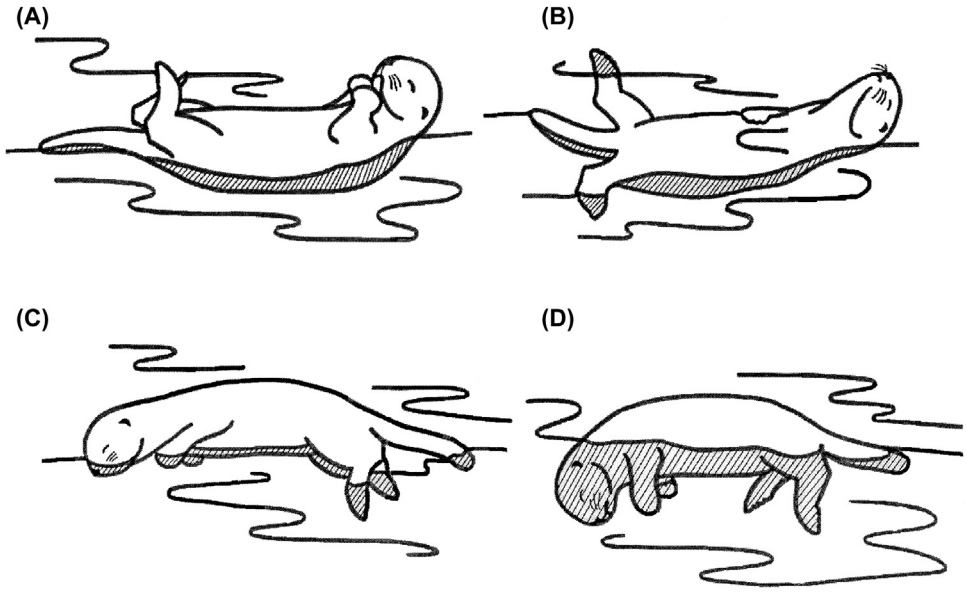


**Figure 6** Typical sleep postures of sea otters sleeping in the water. (A) During quiet sleep (QS), sea otters float on their back with their head and limbs held out of the water. (B and C) During the transition from QS to active sleep (AS) a loss of muscle tone causes the head and limbs to drop and the otter to roll over. (D) During AS the otter floats on its belly with the nostrils below the surface. Reprinted with permission from Lyamin, O.I., Oleksenko, A.I., 2000. Behavioral sleep in captive sea otters. Aquat. Mamm. 26, 132–136, Copyright 2000, courtesy of Kathleen M. Dudzinski.

Otariidae) can keep their nostrils above the surface by floating on their side while paddling one flipper during unihemispheric or asymmetric QS. However, during AS, paddling stops and their head sinks below the surface. As a result, fur seals greatly reduce the time spent in AS when forced to sleep in the water. Rather than reducing the time spent in AS, true seals and manatees solve this problem by simply holding their breath during AS. Interestingly, it is less clear whether AS is present in cetaceans. Although an early study of a pilot whale (*Globicephala scammoni*) reported AS with EEG activation, all subsequent EEG studies of cetaceans failed to detect EEG or behavioral signs of AS, calling into question whether cetaceans exhibit AS (Lyamin et al., 2008). Nonetheless, infrequent twitching has been observed in uninstrumented cetaceans resting with their eyes closed on the bottom of their tank (Lyamin et al., 2002). In a gray whale (*Eschrichtius robustus*), twitching was associated with listing to one side, suggesting reduced muscle tone (Lyamin et al., 2000). Sperm whales (*Physeter macrocephalus*) in the wild have also been observed unresponsive while floating vertically in the water column, a posture attained passively due to increased buoyancy of the head relative to the rest of the body (Miller et al., 2008). Although observations of eye movements and twitching were not made, this posture is suggestive of muscle atonia and therefore might reflect AS. Collectively, these studies suggest that although AS may be greatly reduced in some marine mammals, at least some AS with reduced muscle tone is retained.

In birds, AS is also accompanied by behavioral signs of reduced muscle tone, such as drooping of the head and wings. QS can occur with one (eg, ducks; Rattenborg et al., 1999, 2000) or both (eg, ostriches and owls) eyes open (Lesku et al., 2011), whereas both eyelids close during AS, possibly also reflecting a reduction in muscle tone. As in mammals, reduced muscle tone also contributes to the cessation of some thermoregulatory behaviors (eg, shivering and panting) during avian AS (Graf et al., 1987). Despite behavioral signs of reduced muscle tone in birds, nuchal EMG recordings rarely show signs of atonia. In geese, this may reflect an ability to actively maintain some tone during AS (Dewasmes et al., 1985). When geese slept with their head supported on their back they showed atonia during AS, but when they slept with their head facing forward and unsupported, some muscle tone was maintained (**Fig. 7**). As observed in other birds, this resulted in the head drooping in a slow, seemingly controlled manner, rather than in a free fall. Interestingly, this control appears to be regionally specific, as muscle groups controlling the posture of various body parts (head, wings, feathers) may show differential signs of reduced tone (Rattenborg, pers. observ.). Also, in birds that sleep while standing (eg, ducks, geese), balance is usually maintained during AS even though head movements show signs of reduced muscle tone. Collectively, this strategy to maintain postural control during AS suggests that reduced muscle tone is a fundamental component of AS; if it were not, birds should have simply done away with it altogether.

In addition to reduced muscle tone and twitching during AS, forebrain activation is present in nearly all mammalian and avian species examined thus far. Possible exceptions to this "rule" include monotreme mammals (echidna and platypus) and ostriches. Monotremes represent an early branch of the mammalian tree that diverged from therian mammals (placentals and marsupials). Similarly, ostriches, along with emus, rheas, tinamous, and kiwis, are members of an early branch of the avian tree (Palaeognathae). Because monotremes and Palaeognathic birds retain several primitive traits (eg, egg laying in monotremes), they may also retain primitive sleep traits, thereby providing insight into the evolution of QS and AS.

In the first two studies of echidnas (*Tachyglossus aculeatus*), only EEG (slow waves) and behavioral signs of QS were detected (Allison et al., 1972; Siegel et al., 1996). Despite the absence of AS-like EEG activation and twitching, Siegel et al. (1996) found that brain stem neuronal activity showed an irregular pattern similar to that observed in placental mammals during AS. This suggested that the ancestral sleep state for mammals consisted of cortical slow waves occurring in conjunction with AS-like activity in the brain stem. In contrast, Nicol et al. (2000) reported EEG activation accompanied by REMs in

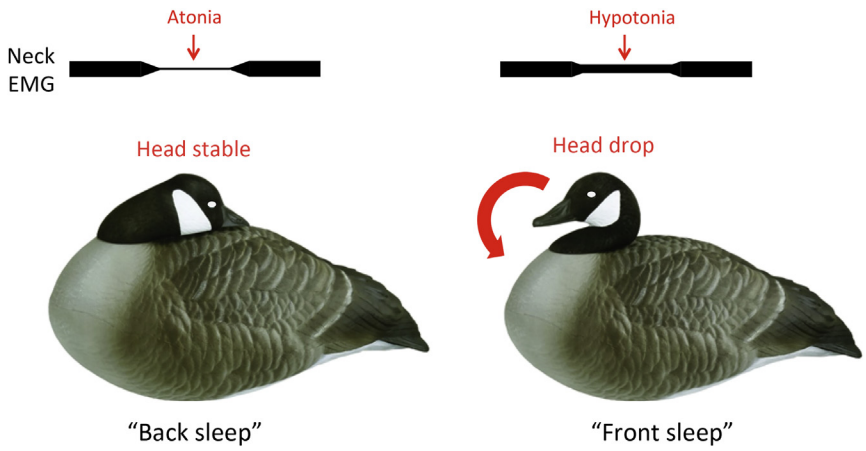


**Figure 7** Behavioral control of muscle tone during active sleep (AS) in geese. Geese can sleep with their head supported on their back (back sleep) or with their head unsupported, facing forward (front sleep). During back sleep, mammalian-like muscle atonia is observed in the neck electromyogram (EMG), whereas during front sleep, some muscle tone is maintained (hypotonia) resulting in a gradual, controlled drop of the head. This ability to maintain some muscle tone during AS appears to be a general feature of birds. Based in part on Dewasmes, G., et al., 1985. Polygraphic and behavioral study of sleep in geese: existence of nuchal atonia during paradoxical sleep. Physiol. Behav. 35 (1), 67–73.

echidnas housed under certain temperatures and proposed that unnatural temperatures had suppressed AS in the earlier studies. Although this controversy remains unresolved, Siegel's study of the platypus (*Ornithorhynchus anatinus*) also suggested that monotremes exhibit unusual sleep traits (Siegel et al., 1999). The platypus' sleep consisted of large amounts of AS characterized by REMs and other pronounced forms of twitching. Nonetheless, the platypus EEG usually showed slow waves characteristic of QS in therian mammals. Consequently, even though some controversy remains regarding the nature of sleep in echidnas, the platypus seems to exhibit a mixed sleep state that combines features of QS and AS.

A recent study revealed a mixed platypus-like sleep state in ostriches (Lesku et al., 2011). During QS, the ostriches slept with their eyes open and their head held up in a periscopic manner. During AS their eyelids closed, their eyes moved rapidly, and their head drooped, often in association with atonia of the nuchal muscles. Although the EEG occasionally showed activation similar to that observed during AS in other birds, most of the other AS features occurred in conjunction with EEG slow waves, much like that observed in the platypus. Also like the platypus, when the time spent in AS was based only on non-EEG components, ostriches had unusually large amounts of AS for a bird. Although additional Palaeognathic birds should be examined, and the controversies in the monotreme literature need to be resolved, the available evidence suggests that the cooccurrence of brain stem and forebrain aspects of AS evolved more recently and separately in mammals and birds. If so, this suggests that AS functions associated with reduced muscle tone and twitching preceded the evolution of forebrain activation.

This brief survey of sleep diversity should be sufficient to convince even the most human-centered sleep researcher of the value of the comparative approach. Of course, many important outstanding issues remain. But one very important lesson from these and other comparative studies is that the primary sleep states—AS and QS—are composed of sleep components that are highly malleable across evolutionary time. Rather than searching for which species or groups "have" AS or QS, greater emphasis should be placed on the evolution of the individual components that comprise them (Blumberg, 2013).

### 3.28.5 Lessons From Developmental Studies of Sleep

Along with the unquestionably strong bias toward investigating sleep in mammals, there is an equally strong bias toward investigating sleep in adults. The fact that such a bias toward adult sleep exists at all is odd given the fact that one of the undisputed universal features of sleep is that it predominates in early development. This is true in mammals (Blumberg and Seelke, 2010; Jouvet-Mounier et al., 1970; Roffwarg et al., 1966; Shimizu and Himwich, 1968; Gramsbergen et al., 1970) and birds (Scriba et al., 2013a), as well as zebrafish (Sorribes et al., 2013) and flies (Kayser et al., 2014; Shaw et al., 2000). In addition, in mammals and birds, AS is highest early in life and declines as the animal matures toward adulthood (**Fig. 8**; Scriba et al., 2013a; Roffwarg et al., 1966; Jouvet-Mounier et al., 1970; Lesku and Rattenborg, 2014).

It can reasonably be argued that the search for the developmental origins of sleep, in vertebrates and invertebrates, may be the surest path to revealing its phylogenetic origins (Corner and van der Togt, 2012; Corner, 2013a). For many years, Michael Corner promoted this idea by focusing on the roots of sleep and wakefulness in the earliest motility cycles exhibited by vertebrate and invertebrate embryos. These cycles, consisting of spontaneous (ie, not reflexive) bursts of motor activity observed in chick and rat embryos (Hamburger, 1963; Narayanan et al., 1971), were considered by Corner to be direct developmental precursors of sleep. He wrote: "Trains of generalized phasic 'rapid body movements', observed during the first few weeks after birth in sleeping chicks and rats, suggest that sleep motility reflects the continued postnatal expression of neural mechanisms responsible for primordial motor patterns operative in the early stages of development and evolution" (p. 292) (Corner, 1977).

Corner's views about the intertwining of sleep development and evolution were ahead of their time. After all, for much of the 20th century, evolutionary biology turned its back on development as a contributor to our understanding of evolutionary processes. That attitude has changed dramatically in recent decades with the emergence of evolutionary developmental biology (evo devo) (Carroll, 2006; Arthur, 2011; West-Eberhard, 2003; Blumberg, 2009), which has revived the notion that evolution occurs through the modification of developmental processes. For a variety of reasons, such ideas have yet to be appreciated widely within the field of sleep research. However, if we are to gain a full understanding of the evolution of sleep, the adoption of a developmental comparative approach is essential (Blumberg, 2013).

The propensity for animals to sleep more in early development demands an explanation. Unfortunately, conventional comparative approaches to sleep are unlikely to provide that explanation. For example, as sleep measures across diverse species have accumulated, many attempts have been made to associate these measures with such physiological and life history variables as gestation length, longevity, metabolic rate, neonatal and adult brain weight, and risk of predation (Zepelin and Rechtschaffen, 1974; Lesku et al., 2006; Capellini et al., 2008; Siegel, 2005). Much has been learned using such statistical approaches, but they have severe limitations for understanding development. For example, Capellini et al. (2008) noted across a variety of species that there was no statistical association between REM sleep durations measured in adults and neonatal brain weight. Based on this lack of an association, they suggested that "the major role of REM sleep is not linked to brain development" (p. 1772). But such a suggestion requires that one takes seriously the idea that any static measure (in this case, neonatal brain weight) can adequately represent a *process* like development. Developmental processes unfold over spatial and temporal scales that lie beyond what can be captured by such a crude measure as neonatal brain weight. Think, for example, about the role that sleep plays in modulating plasticity in visual neocortex (Frank et al., 2001) or that myoclonic twitching is thought to play in the activation of developing sensorimotor neural circuits (Blumberg et al., 2013). Why would one expect such processes to be associated in any way with neonatal brain weight?

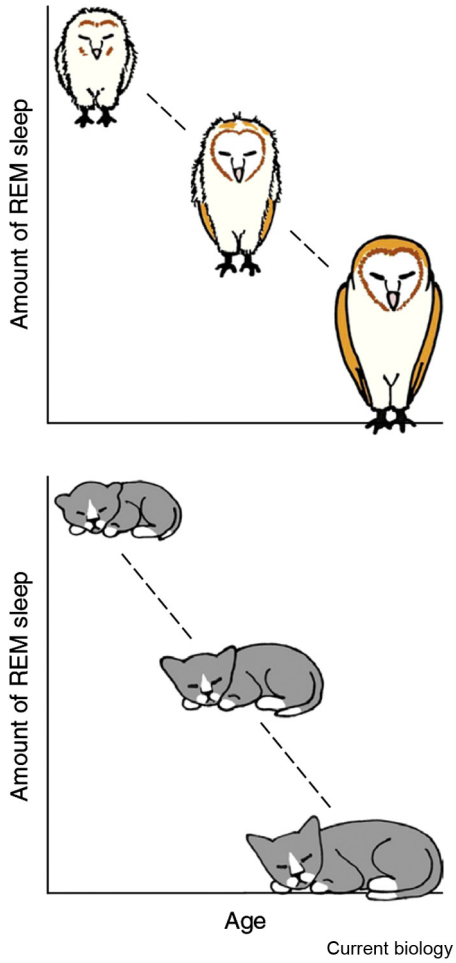


**Figure 8** Age-related decline in active sleep [AS or rapid eye movement (REM) sleep] in barn owls (top) and kittens (bottom). Absolute values not shown. Reprinted with permission from Lesku, J.A., Rattenborg, N.C., 2014. Avian sleep. Curr. Biol. 24 (1), R12–R14. Copyright 2014, Elsevier Ltd.

Another approach to assessing the developmental importance of sleep is to search for species that violate expectations. For example, a decade ago it was reported that newborn killer whales (*Orcinus orca*) and bottlenose dolphins (*Tursiops truncatus*) exhibit extremely low levels of sleep behavior over the first several postpartum weeks (Lyamin et al., 2005). Several times throughout their short article, the authors couch their findings as addressing the possibility that "sleep behaviour may not have the developmental and life-sustaining functions attributed to it" (p. 1177).

Although subsequent work has questioned Lyamin et al.'s findings, at least in bottlenose dolphins (Sekiguchi et al., 2006), here we ask whether any such findings in these marine mammals provide a strong foundation for testing broader theories about the importance of sleep for developing mammals. Comparative assessments are indeed very useful for testing evolutionary theories, but the species chosen for the comparison must be matched appropriately to the question under consideration. For example, if someone were to claim that the visual system is *necessary* for the survival of all mammalian species, defeating this claim would require little more than presenting the subterranean blind mole rat (genus *Spalax*) as a counterexample. In contrast, it would not be valid to claim that the very existence of the blind mole rat argues against the importance of the visual system for all other mammals. Accordingly, even if it were true that whales and dolphins sleep very little in the early postnatal period, such a finding would not necessarily be relevant to the question of whether sleep is functionally important for other mammalian species.

But it is also important to stress that development does not begin at birth. This fact is true whether a species is altricial—that is, born in a relatively immature state—or precocial—that is, born in a relatively mature state. Whales and dolphins are highly precocial mammals that have long gestation lengths for mammals of their body weight (Martin et al., 2005). Rats are altricial species with gestation lengths of 21 days that nonetheless exhibit sleeplike behavior beginning approximately 4 days before birth (Narayanan et al., 1971; Robinson et al., 2000). The same is true for domestic sheep, but because they are precocial they exhibit sleep as fetuses beginning many weeks before the end of their 150-day gestation period (Karlsson et al., 2010). Now consider that bottlenose dolphins and killer whales have gestation lengths of approximately 12 and 15 months, respectively. That is quite a long time for sleep to play out its hypothesized developmental role, regardless of what that role may be. Thus, although it is undoubtedly of great

value to know how newborn mammals of different species adjust their sleep patterns depending on their ecology and life history, we should exercise great caution when using comparative analyses to test specific hypotheses about the functions of sleep.

For testing developmental theories about sleep, we need more studies that focus on real-time developmental changes in sleep. But developmental analyses do more than simply reveal the importance of development for sleep: developmental analyses—just as we saw with comparative analyses—expand our vision, providing opportunities for testing and challenging ideas about the evolution and functions of sleep.

#### 3.28.5.1 Development of Ultradian and Circadian Sleep–Wake Rhythms

One of the key defining features of infant sleep is its fragmentation. This fragmentation was demonstrated in human infants many decades ago: newborns are awake and asleep in short bouts that are equally dispersed throughout the day and night, with these bouts consolidating gradually until, when infants are about 3–4 months of age, wake and sleep bouts begin to cluster during the day and at night, respectively (Kleitman and Engelmann, 1953). In newborn rats, which are smaller and more altricial than human infants, individual sleep and wake bouts often last less than 15 s, resulting in extraordinarily rapid sleep–wake cycling across the day and night (Karlsson et al., 2004; Blumberg et al., 2005). Over the first two postnatal weeks, sleep and wake bouts consolidate as brain stem and forebrain structures—including the locus coeruleus (LC), dorsomedial hypothalamus (DMH), and suprachiasmatic nucleus (SCN)—become anatomically and functionally integrated (Gall et al., 2012). By the end of the second postnatal week, infant rats begin to exhibit circadian distributions of sleep and wake bouts that are the opposite of those seen in humans (rats being nocturnal, humans diurnal; Gall et al., 2008).

There are two basic levels—both of them involving motor systems—at which to consider sleep–wake cycling in early development. One was discussed earlier and involves cyclic bursts of motor activity that, in newborn rats, are easily classified into two broad classes: high-amplitude and often coordinated movements that are indicative of wakefulness (eg, kicking, stretching, yawning) and brief, jerky, discrete movements that are indicative of active sleep (ie, myoclonic twitches). The backdrop to these motor events is ultradian cyclicity in muscle tone (*ultradian* refers to cycles that occur more than once each day); that is, wake movements are produced against a background of high muscle tone and twitches are produced against a background of muscle atonia (see Fig. 9A). Thus, in newborn rats, these two dimensions of motor activity cohere to present organized sleep–wake states.

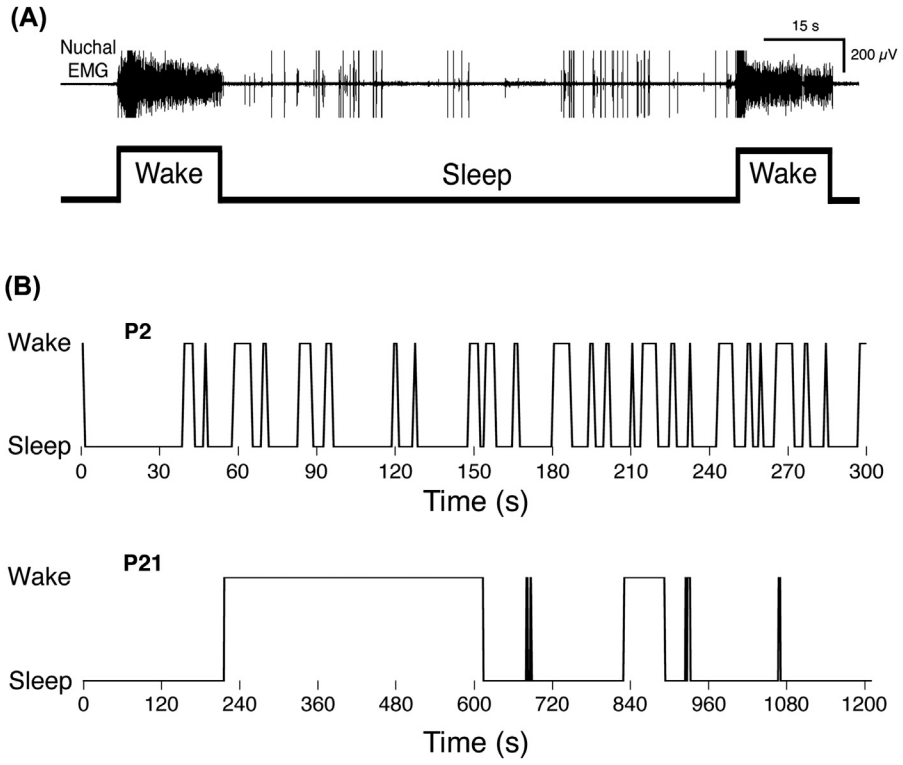


**Figure 9** Developmental changes in sleep consolidation in Norway rats. (A) Top: A 2.4-min record in a P8 rat of nuchal electromyogram (EMG) showing two brief periods of high nuchal muscle tone (indicative of wakefulness) separated by a longer period of muscle atonia (indicative of sleep). The sharp spikes in the EMG record during sleep are myoclonic twitches. Bottom: Categorization of states based on the EMG record. (B) Cycling between sleep and wake in a P2 and P21 rat. Note the different timescales in the two traces. Reprinted with permission from Blumberg, M.S., et al., 2005. Dynamics of sleep-wake cyclicity in developing rats. Proc. Natl. Acad. Sci. U.S.A. 102, 14860–14864, Copyright 2005, American Psychological Association.

Focusing on muscle tone alone, we can discern another level of structure—this one statistical. Specifically, when we precisely measure the duration of many sleep and wake bouts and examine their statistical distributions across age, we find that the sleep bouts of pups at the earliest ages distribute randomly (Fig. 10A), as do the wake bouts (Blumberg et al., 2005; Gall et al., 2008; Fig. 10B). Over the first two postnatal weeks, this statistical structure does not change even as the initially fragmented bouts consolidate into longer and longer ones. But then, at the end of the second postnatal week, the previously random structure of wake bouts

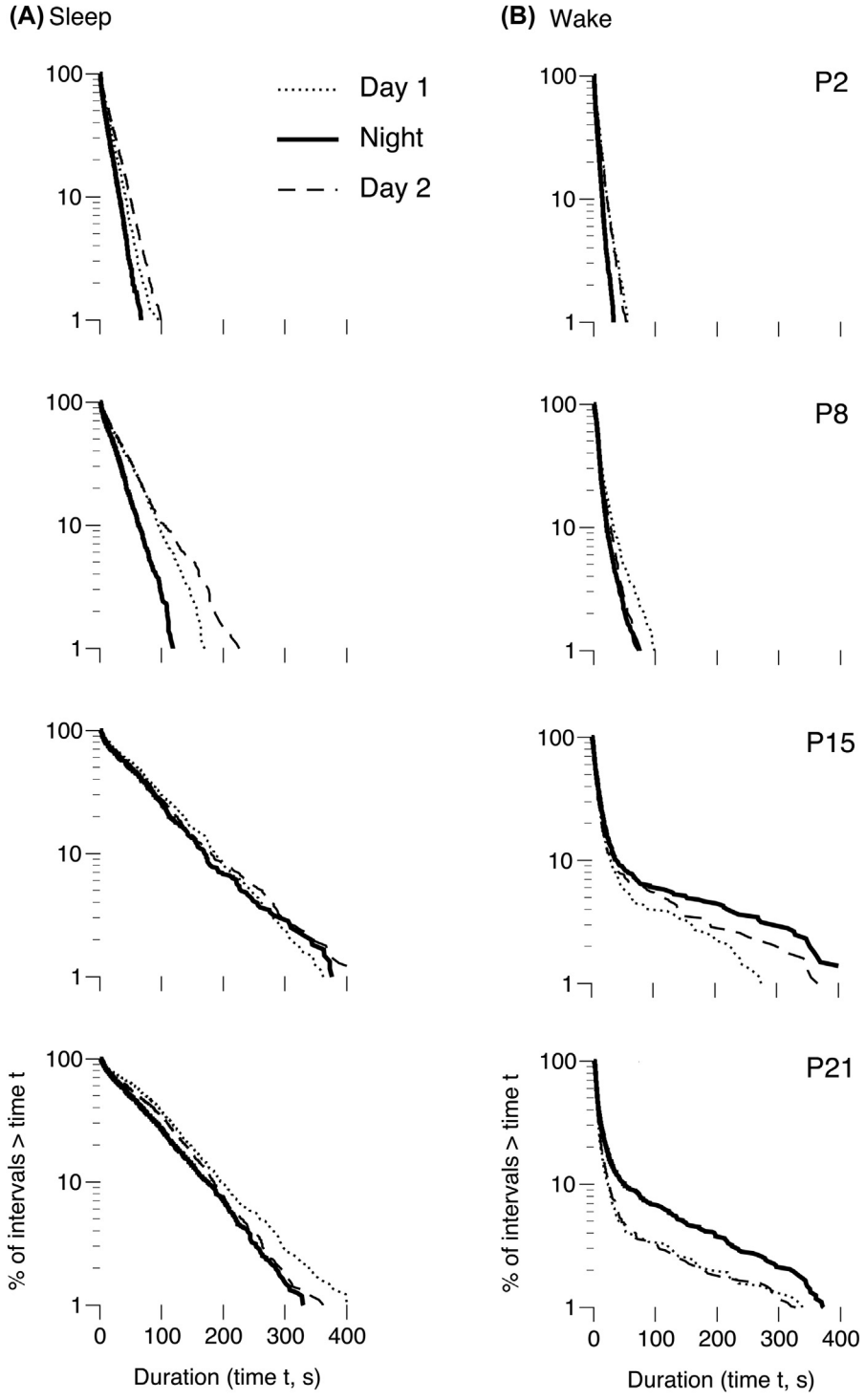


**Figure 10** Log-survivor plots of (A) sleep and (B) wake bout durations for nocturnal Norway rats at P2, P8, P15, and P21 on day 1 (*dotted line*), at night (*solid line*), and on day 2 (*dashed line*). *Straight lines* on these semilog plots indicate that the data follow an exponential distribution. Adapted from Gall, A.J., et al., 2008. The development of day–night differences in sleep and wakefulness in Norway rats and the effect of bilateral enucleation. J. Biol. Rhythms 23, 232–241, Copyright 2008, Sage Publications.

transforms into a new one characterized by a small proportion of exceedingly long wake bouts; this new structure has been described as a power-law distribution. Importantly, sleep bouts do not undergo this power-law transformation. Moreover, these statistical features of sleep and wake bouts are seen in *adult* rats, mice, cats, and humans (Lo et al., 2004), although the bout structures for humans are less clear (Arnardóttir et al., 2010).

The structure and development of sleep and wake bouts provides the foundation for additional insights into the mechanisms of sleep and their modulation through evolution. For example, whereas cross-species comparisons typically focus on the accumulated durations of sleep across the day and night, in polyphasic species (which comprise the vast majority of mammals and birds) these durations are accumulated individual bout by individual bout. Thus, if we wish to understand species differences in sleep, we cannot ignore the processes that mediate *transitions* between sleep and wake states. Moreover, the mechanisms that mediate those transitions are one of the likely targets of evolutionary modifications to sleep and wake states.

So far, the development of sleep and wake bouts has been investigated in Norway rats (*Rattus norvegicus*; for review, see Blumberg et al., 2014), wild-type and knockout orexin mice (Blumberg et al., 2007), and Nile grass rats (Todd et al., 2012). Norway rats have proven very useful for exploring the neural mechanisms underlying developmental changes in sleep–wake structure. For example, in week-old rats, complete surgical separation of the brain stem from the forebrain does not prevent pups from exhibiting organized and integrated cycles in motor behavior and muscle tone that resemble those in intact pups (Kreider and Blumberg, 2000; Karlsson et al., 2004). This finding indicates that early in development there exists, within the brain stem alone, neural circuits that are sufficient to produce integrated sleep–wake cycles, which is inconsistent with the hypothesis that the fundamental sleep–wake "flip-flop" spans brain stem and hypothalamic circuits (Saper et al., 2001).

One intriguing feature of the early oscillator is that sleep and wake bouts are independent of each other. Such a notion is counterintuitive if one thinks of sleep and wake as two sides of the same coin. But, in fact, the processes that govern sleep and wake bouts are statistically independent of one another and exhibit unique developmental trajectories (Blumberg et al., 2005). Moreover, they can be manipulated independently through lesions of select brain regions; for example, lesions of the DMH or SCN in 8-day-old rats result in the fragmentation of wake bouts—but not sleep bouts—by 21 days of age (Gall et al., 2012). Similarly, chemical lesions of the LC prevent the developmental emergence of power-law wake behavior at 21 days of age, but have no effect on sleep bouts (Gall et al., 2009). Computational models of the infant sleep–wake oscillatory system, based on relatively simple networks of mutually inhibitory neurons, are able to mimic this independence of sleep and wake bouts and capture their statistical structure as well (Patel, 2016).

In Norway rats, the developmental emergence of a power-law structure to wake bouts accompanies the emergence of nocturnal wakefulness (Gall et al., 2008). Specifically, wake bouts exhibit a significant shift at the end of the second postnatal week such that they develop longer durations at night (**Fig. 10B**). This observation provided the impetus for a systematic developmental comparative analysis of sleep–wake cycling in nocturnal Norway rats and diurnal Nile grass rats and associated neural differences (Todd et al., 2012). Because the SCN is more active during the day in all of the nocturnal and diurnal mammals studied thus far, the SCN cannot be responsible for nocturnality and diurnality. Therefore, we focused instead on the retinohypothalamic tract (RHT) and the interactions between the SCN and its close functional neighbor, the ventral subparaventricular zone (vSPVZ). First, we found very similar developmental patterns in sleep and wake bouts in the two species until the end of the second postnatal week, when wake bouts alone diverged in the two species such that wake bouts were longer at night in the Norway rats and wake bouts were longer during the day in the Nile grass rats (*compare* **Figs. 10A** and **11**). Around the same time as this behavioral change, the activity patterns in the SCN and vSPVZ diverged such that the two structures exhibited in-phase activity profiles across the day and night in Norway rats, but antiphase activity profiles in the grass rats. Next, we were able to link these neural activity profiles to differential development of RHT connectivity to the two structures. Finally, a survey of the literature on 14 mammalian species revealed an intriguing pattern of RHT → vSPVZ connectivity that could help to explain species differences in circadian phase preference.

Based on these comparative observations, we hypothesized that species differences in a fundamental life history variable—circadian phase preference—arise through developmental rewiring of connectivity among the RHT, SCN, and vSPVZ. Of course, there are likely multiple paths to nocturnality and diurnality in mammals and other groups. Regardless, this application of the developmental comparative approach to the problem of circadian phase preference illustrates its power to reveal neural mechanisms and developmental pathways that are potential targets of selection.

#### 3.28.5.2 Developmental Emergence of Cortical Slow Waves

As discussed in Section 3.28.4.1, cortical slow waves (or delta waves) are a defining feature of QS in adult mammals and birds. Moreover, delta waves provide the foundation upon which many theories of sleep function have been built, including those that focus on memory consolidation (for review, see Diekelmann and Born, 2010). Delta waves also provide the metric—delta power—that is commonly used to assess the intensity of rebound sleep and its dissipation during postdeprivation sleep rebound (see Rechtschaffen et al., 1999; Borbély et al., 2016).

Delta waves in adult mammals arise from complex interactions between thalamic and cortical circuits (Steriade, 2006). However, in young mammals, delta waves arrive relatively late on the scene: in rats, for example, they are only weakly detectable at P11, and they gain steadily in power over the next several days (Seelke and Blumberg, 2008; Frank and Heller, 1997). What this means is that measurements of sleep before P11 cannot rely on the occurrence of delta waves or, for that matter, any other conventional EEG feature for distinguishing sleep and wake states (Blumberg and Seelke, 2010). Such is the centrality of the EEG

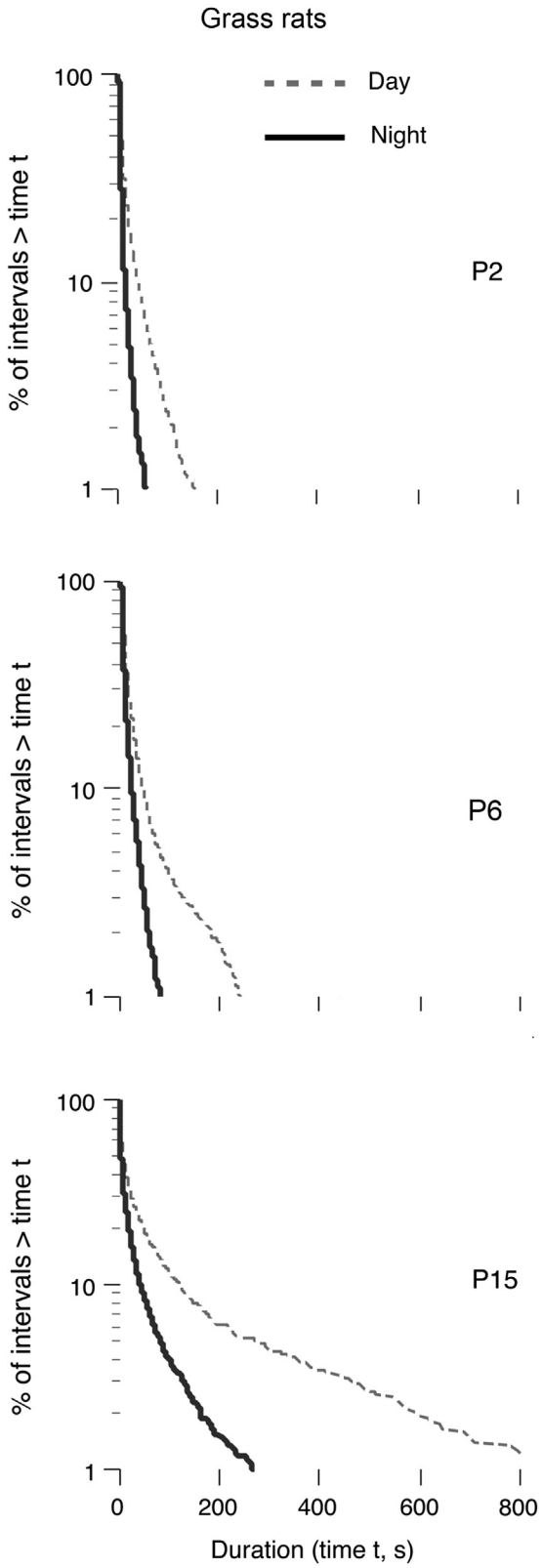


**Figure 11** Log-survivor distributions of wake bouts in diurnal Nile grass rats. Recordings were made during the day (*dashed line*) and night (*solid line*) at P2, P6, and P15. Note the substantial increase in diurnal wakefulness between P6 and P15. Adapted from Todd, W.D., et al., 2012. Distinct retinohypothalamic innervation patterns predict the developmental emergence of species-typical circadian phase preference in nocturnal Norway rats and diurnal Nile grass rats. J. Comp. Neurol. 520, 3277–3292, Copyright 2012, John Wiley and Sons.

to modern sleep research that the absence of reliable EEG indicators of sleep in early infancy led some to doubt the existence of sleep before P11 (Frank and Heller, 2003). One possible extension of this latter view is that the developmental emergence of delta waves at P11 should be accompanied by a large, qualitative transition in sleep–wake organization. Recall that in rats during the first postnatal week, there are rapid transitions between periods of high muscle tone with accompanying high-amplitude, coordinated movements, and periods of atonia with accompanying myoclonic twitches. Moreover, interposed between periods of wake movements and twitches are periods of behavioral quiescence against a background of decreasing muscle tone or atonia—that is, quiet wakefulness transitions to quiet sleep. Does this basic sleep–wake structure change in any momentous way at P11 when the first delta waves emerge (Seelke and Blumberg, 2008)? In fact, it does not: instead, the early-emerging delta waves simply fit into the QS "slot" that precedes the onset of twitching that defines each AS bout (**Fig. 12**). Moreover, during prolonged AS bouts in which bursts of twitching wax and wane, delta waves occasionally occur during those intervening periods, only to disappear again when twitching recommences.

This study showed that, although EEG activity provides valuable information regarding state-dependent functioning of forebrain structures, the fundamental structure of sleep–wake states has long been established by the time that delta waves first emerge at P11. And that fundamental structure derives largely from network processes within the brain stem, not the forebrain. Indeed, one of the notable changes in the development of the sleep–wake system entails increased bidirectional communication between brain stem and forebrain structures (including the hypothalamus) involved in sleep–wake regulation over the first postnatal week (Gall et al., 2012; Todd et al., 2010).

A broader lesson to be learned from the late emergence of delta activity is that we should be cautious about assigning essential or privileged status to any single component of sleep (Blumberg and Lucas, 1996). Returning to the theme with which we began this chapter, sleep is first and foremost a behavioral state. Within this behavioral context, sleep can comprise any of a number of components, including cortical delta waves and spindles, hippocampal theta, pontine waves, irregular respiration, unihemispheric sleep, penile tumescence, cessation of thermoregulation, REMs, and other forms of twitching in limbs, whiskers, and bills. Species will differ in the expression of these components because species differ with respect to their morphologies, neural structures, and neural connectivity. A truly comparative science of sleep will seek to understand these components, their unique developmental and evolutionary histories, and their functional contributions (Blumberg, 2013).

### 3.28.5.3 Myoclonic Twitching

As has already been noted, twitches are a defining feature of AS and, along with bodily relaxation, the most prominent behavioral component of sleep. Twitches arise exclusively from striated muscle, resulting in brief, jerky, and discrete movements that are easily distinguishable from the high-amplitude, prolonged, smooth, and often coordinated movements of wakefulness. Although twitches have long been relied upon for identifying the state of AS, consideration of their possible functional significance has largely been obscured by a traditional perspective that views twitches as mere epiphenomena of a dreaming brain. According to this perspective, dreams would be fully enacted if not for the medullary mechanism that inhibits movements during sleep; but since this inhibitory mechanism is imperfect, some movements are able to "leak through," and it is these remnants of dreams that we observe as twitches. There are, however, many reasons to discount this perspective, not least of which the fact that complete disconnection of the brain stem and forebrain does not prevent the continued expression of twitching (see Blumberg and Plumeau, 2016).

Once we set aside the epiphenomenal perspective on twitching, a host of possibilities present themselves. Foremost among them is the possibility that twitching, rather than being a by-product of the sleeping brain, is actually a product with a specific function (Blumberg et al., 2013). Any functional hypothesis, however, must account for the fact that twitches are discrete and jerky

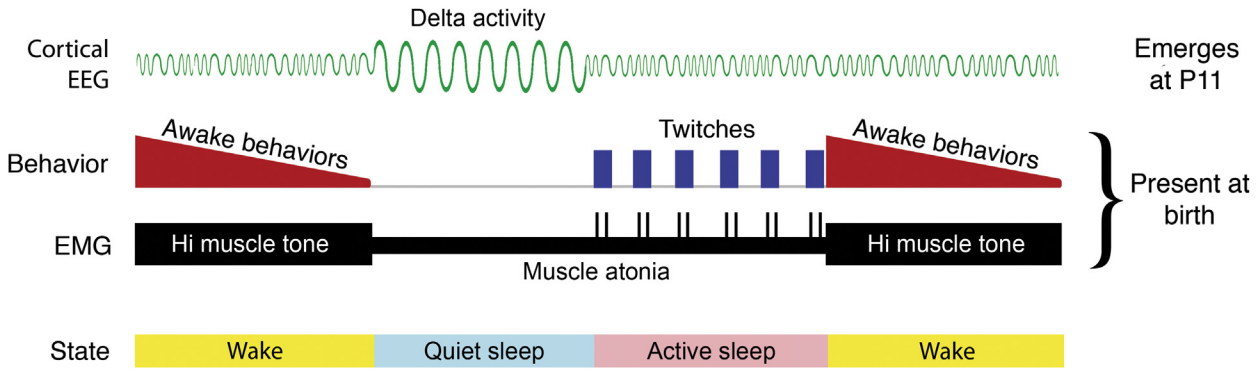


**Figure 12** Illustration of a typical sleep–wake cycle in the early postnatal period in Norway rats. Bottom row: Categories of behavioral state. Middle two rows: Electromyographic (EMG) and behaviorally observable components of the cycle. Top row: Beginning at P11, the cortical electroencephalogram (EEG) begins to exhibit delta activity. Even at P11, delta is expressed primarily during the period defined at earlier ages—based on EMG recordings and behavior alone—as quiet sleep. Reprinted with permission from Blumberg, M.S., Gall, A.J., Todd, W.D., 2014. The development of sleep–wake rhythms and the search for elemental circuits in the infant brain. Behav. Neurosci. 128, 250–263, Copyright 2014, American Psychological Association.

movements produced exclusively during AS, that they are most prevalent early in development, and that they variably persist into adulthood depending on the limb and the species. Unfortunately, due to the long history of interpreting twitches as by-products of the sleeping brain, there is scant information about the quantity and patterning of twitching across the life span in any species.

Twitches are perhaps best viewed as the sensorimotor system's version of spontaneous activity. Spontaneous activity is a robust feature of other developing sensory modalities (for review, see Kirkby et al., 2013). For example, in the visual system, waves of activity in the ganglion cell layer of the retina produce robust input to visual areas in the thalamus, neocortex, and midbrain. In the auditory system, the cochlea is also spontaneously active, although the downstream effects of this activity are less well understood. Twitches may be unique in that they occur exclusively during sleep; but given that sleep is widely considered a state of sensory disconnection (Tononi and Cirelli, 2014), it was possible that any sensory feedback from twitching would be blocked from entering the nervous system. In fact, based on work using infant rats, the opposite is true: twitch-related sensory feedback triggers neural activity throughout the neuraxis, from spinal cord to the medulla, midbrain, cerebellum, thalamus, neocortex, and hippocampus (eg, Petersson et al., 2003; Khazipov et al., 2004; Mohns and Blumberg, 2010; Tiriac et al., 2012, 2014; Sokoloff et al., 2015; Del Rio-Bermudez et al., 2015). Moreover, in contrast with wake movements, twitches trigger immense amounts of sensory feedback to the developing brain (Tiriac et al., 2014).

That twitches trigger modality-specific neural activity, are produced as discrete events, and occur against a background of muscle atonia make them ideally suited to develop and maintain sensorimotor neural circuits (Blumberg, 2015; Blumberg et al., 2013). During development, when twitching is most abundant, there are many activity-dependent processes in neocortex and other brain areas that are likely to be driven or modulated by the sensory consequences of twitching, including neurogenesis, cell death, cell migration, neuronal differentiation, and the development of functional neural networks (Kilb et al., 2011).

With respect to the possible contributions of twitching to the maintenance of neural circuits and their repair after injury or disease, much less is known. But there are reasons to believe that twitching—unlike spontaneous activity in the visual and auditory systems—might have such additional functions. First, from a functional perspective, the sensorimotor system is obviously different from the visual auditory systems in that its very name implies integration of inputs and outputs. Such sensorimotor integration must be continually calibrated and updated as limbs develop and as new skills are learned. Accordingly, if twitches play a role in sensorimotor integration early in development (Del Rio-Bermudez et al., 2015), we might expect it to continue playing that role into adulthood.

Second, unlike spontaneous retinal and cochlear activity, twitching persists into adulthood, perhaps reflecting the possible ongoing functions of twitching described previously. For example, in highly visual species like humans and cats, REMs are a reliable indicator of phasic AS across the life span; in rats, which develop a highly precise and dedicated whisker sensorimotor system, the whiskers twitch in the newborn (Tiriac et al., 2012); anecdotally, whiskers continue to twitch during AS throughout adulthood. In the adult platypus, it is the sensory-rich bill that twitches a lot (Siegel et al., 1999). Although good quantitative and comparative assessments of twitching in these systems is lacking, there are sufficient clues to suggest the hypothesis that the relative importance of a sensorimotor appendage to a given species will be reflected in the amount of twitching observed in the adults of that species (Tiriac and Blumberg, 2016). This hypothesis could be tested by associating twitching with the relative amount of cortical tissue devoted to each sensory modality (Krubitzer, 2007).

What is needed, then, is a developmental comparative science of twitching—one that relates the development and use of species-typical sensorimotor appendages to the neural representations of those appendages in cortical (and subcortical) brain areas. Accordingly, it is predicted (for example) that fingers in humans, the multiappendage star in star-nosed moles, the muscle-rich trunk of elephants, the prehensile tail of New World monkeys, the gripping feet of raptors, and the probing tongue of woodpeckers will exhibit high rates of AS-related twitching in relation to other parts of the body as their functionality emerges through development and continues into adulthood (Tiriac and Blumberg, 2016).

### 3.28.6 Conclusions

Like hibernation and torpor, sleep has evolved within the context of extensive species differences in physiology, morphology, ecology, and life history. Nonetheless, a tension remains between those who believe that there is a universal function of sleep that has yet to be discovered and those who believe that sleep reflects the multifaceted adaptations of species to their ecological contexts (see Siegel, 2009). Of course, there are gradations that lie between these two extremes: as with the waking state, there may be many functional sleep processes that range from the universal to the near-universal to the highly species specific.

Moreover, characterizing any given functional sleep process as universal or species specific can be more complicated than it may initially appear. For example, consider one intensively investigated component of sleep—sleep spindles—that has been implicated in the consolidation of memories within the mammalian neocortex (Diekelmann and Born, 2010). Clearly, anything that is learned about cortical sleep spindles will tell us little about sleep in animals that lack either sleep spindles or a neocortex. On the other hand, evidence that sleep contributes to memory in species as evolutionarily distant as mammals and flies (Donlea et al., 2011) suggests a deep homology in this functional aspect of sleep, perhaps not unlike the deep homology linking vertebrate and insect wings (Shubin et al., 1997). Establishing such a deep homology for sleep and memory—which has yet to happen—would constitute a major accomplishment for the field, but it would not close the book on the mysteries of sleep: sleep is far too complex and involves too many neural and physiological systems to be reduced to any single function or process.

The focus on cross-species similarities in comparative studies of sleep has fueled, and has been fueled by, the search for a universal function of sleep. But the comparative method gains its power through a balanced, unbiased assessment of species similarities and differences—preferably based increasingly on studies of animals in their natural habitats (Rattenborg et al., 2008; Scriba et al., 2013a; Lesku et al., 2012). Moreover, comparative approaches are needed to offset the inordinate, and potentially blinding, influence of model organisms, such as rats and flies, on our perception of sleep mechanisms and functions.

Sleep is a complex amalgam of components that reflect each individual's evolutionary history and ecological circumstances. But also, because individual sleep components emerge and coalesce over developmental time (**Fig. 12**), development provides another avenue for exploring the mechanisms and functions of sleep and sleep–wake cyclicity (Blumberg et al., 2014). For example, the emergence of cortical slow waves at P11 in rats provides the opportunity—not yet explored—to devise novel approaches for investigating their function. In addition, the developmental and functional relationship, if any, between cortical spindle bursts (which predominate in early infancy) and sleep spindles (which emerge later in development) has yet to be systematically explored (Tiriac and Blumberg, 2016).

The biggest mystery of sleep development, however, concerns its predominance in early life. This observation was first highlighted in humans 50 years ago and gave rise to the ontogenetic hypothesis of sleep (Roffwarg et al., 1966). Since then, the predominance of sleep in infancy has been documented in numerous mammalian species (eg, Jouvet-Mounier et al., 1970; Shimizu and Himwich, 1968), as well as owls (Scriba et al., 2013b; Scriba et al., 2013a), zebrafish (Sorribes et al., 2013), flies (Kayser et al., 2014; Shaw et al., 2000), and worms (Raizen et al., 2008). As this seemingly universal feature of sleep is increasingly recognized (Kayser and Biron, 2016), it will become progressively more difficult to ignore development as a critical source of insight into its functions.

If we have learned anything about sleep over the last half century, it is that this behavior is ubiquitous across multiple dimensions of time: the state of sleep appears to be as evolutionarily ancient as the state of wake and individual animals exhibit sleep from their earliest moments of life. Given this ubiquity and despite incredible gains in our knowledge of the phenomenology and mechanisms of sleep, it is perhaps not surprising that the functions of sleep have so far eluded us. After all, anything as ancient and pervasive as sleep has had ample time and opportunity to coopt numerous functions within its domain. Therefore, it is conceivable that the very first adaptive benefit that sleep conferred on an organism is buried too far deep in our evolutionary past—or too intermingled in the machinery of the cell—to ever be revealed. But what is clear today is that we must combine all our tools of investigation—comparative and developmental, descriptive and experimental—if we are to solve the many mysteries of sleep that are now within our reach.

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