Developmental and comparative insights into the origins and functions of sleep

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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—will be vital for revealing the origins and functions of sleep.

Keywords

Active sleep; Altricial; Birds; Brain rhythms; Circadian; Diurnal; Energetics; Evo devo; Invertebrates; Mammals; Nocturnal; Precocial; Quiet sleep; Rapid eye movements; Reptiles; Twitches; Ultradian

Key points

- Sleep exists in all animals investigated, ranging from jellyfish to humans, suggesting that it evolved long ago and plays essential, albeit poorly understood, roles in animal life.
- In several distantly related taxonomic groups, sleep consists of two sleep states that resemble, to some extent, quiet sleep and active sleep found in mammals and birds.
- The neural, physiological, and behavioral components of sleep vary within and between taxonomic groups, complicating attempts to trace the evolution of sleep states.
- Sleep also changes substantially across development, further complicating but also enriching our understanding of the mechanisms, functions, and evolution of sleep.
- The diverse manifestations of sleep provide largely untapped opportunities for examining the unique and shared components that comprise sleep states.

1 Introduction

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.

2 Sleep is a complex behavioral state

First and foremost, sleep is a behavioral state. Indeed, all animals studied thus far exhibit behavioral signs of sleep. Across the day and night, animals seek out and find (or build) suitable resting places, adopt species-typical sleeping postures, and usually remain immobile; they also become less responsive to environmental stimuli, a feature of sleep that distinguishes it from quiet wakefulness. Furthermore, sleep is distinguished from other quiescent states, such as torpor or hibernation, by a quick return to wakefulness when sufficiently stimulated. Finally, when sleep is prevented, animals usually sleep longer and deeper afterward, indicating that it is a homeostatically regulated process.

Sleep behavior has been found in a variety of invertebrates and vertebrates. Among invertebrates, sleep has been described in: Arthropoda, including honey bees (*Apis melifera*; Kaiser and Steiner-Kaiser, 1983), flies (*Drosophila melanogaster*; Shaw et al., 2000; Hendricks et al., 2000a), crayfish (*Procambarus clarkia*; Ramon et al., 2012), and jumping spiders (*Evarcha arcuata*; Rößler et al., 2022); Nematoda (nematodes; *Caenorhabditis elegans*; Raizen et al., 2008); Platyhelminthes (flatworms; *Girardia tigrina*; Omond and Lesku, 2022); Mollusca, including the great pond snail (*Lymnaea stagnalis*; Stephenson and Lewis, 2011), California sea hair (*Aplysia californica*; Vorster et al., 2014), cuttlefish (*Sepia officinalis*; Frank et al., 2012; Corner, 2013a; Iglesias et al., 2019), and octopuses (*Octopus insularis* and *O. laqueus*; de Souza Medeiros et al., 2021; Pophale et al., 2023); and Cnidaria, including jellyfish (*Cassiopea* spp.; Nath et al., 2017) and polyps (*Hydra vulgaris*; Kanaya et al., 2020).

Flies, 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 lifespan changes to sleep in flies and zebrafish that bear similarities to those in mammals, including high quantities of sleep amid fragmented sleep bouts in early life (Shaw et al., 2000; Koh et al., 2006; Sorribes et al., 2013; 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., 2000b; Kayser and Biron, 2016).

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 onset of AS, skeletal muscle tone is actively suppressed, and this "sleep paralysis" is briefly interrupted by jerky twitches of the limbs, digits, eyes, and other appendages such as whiskers, bill, and tail. Although laypeople and scientists alike traditionally viewed these twitches as remnants of dreams, the actual story is more complicated (Blumberg and Plumeau, 2016).

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 in adult mammals and birds captures the slow "delta" rhythm (1–4 Hz) that characterizes QS and the activated wake-like cortical activity that characterizes AS. The presence of wake-like 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 during QS and the rapid eye movements (REMs) of AS. Conventionally, and especially in clinical settings, EMG, EEG, and EOG measures are used to disambiguate the states of wakefulness, QS, and AS in adult mammals, especially humans. However, when investigations turn to infant mammals, non-mammalian vertebrates (e.g., birds, reptiles), or invertebrates (e.g., flies), conventional measures and criteria must be adjusted or even 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 (e.g., 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 progress in these domains 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 expect sleep to have a single function. Rather, we should be seeking the functional value of individual processes or suites of processes that are ideally or exclusively performed during sleep (Blumberg and Lucas, 1996). 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 basic function, 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 Sleep-wake cyclicity and energy allocation

The association of "sleep" with "rest" naturally led investigators to think of sleep as 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 (i.e., 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 Twyver, 1970a); also, the suspension of thermoregulatory processes (e.g., sweating, panting, shivering) during AS is consistent with this view (Graf et al., 1987; Parmeggiani, 1987). In its simplest form, 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 has been 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, 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 compared to wake, 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, italics in the original).

One advantage of Schmidt's energy allocation model 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.

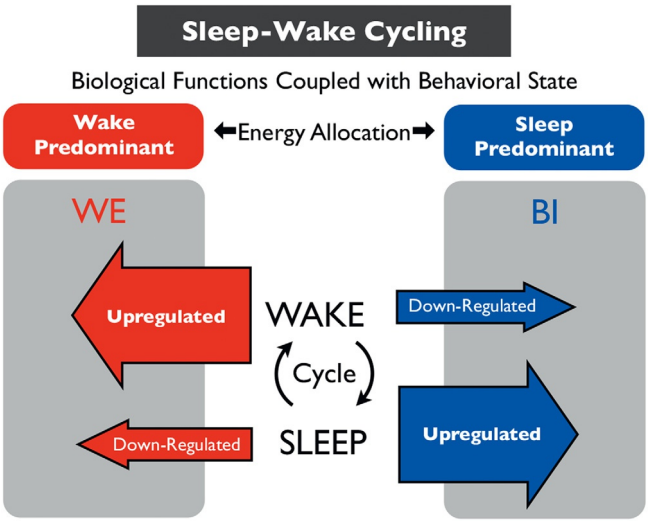

Fig. 1 A schematic depiction of Schmidt's energy allocation model as applied to sleep-wake cycling. According to this model, energy is allocated preferentially to the waking state to support such activities as foraging and reproduction, and allocated preferentially to sleep to support such activities as growth and repair. WE, waking effort; BI, biological investment. Reprinted with permission from Schmidt MH (2014) The energy allocation function of sleep: A unifying theory of sleep, torpor, and continuous wakefulness. *Neuroscience and Biobehavioral Reviews* 47: 122–153, Copyright 2014, Elsevier Ltd.

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 non-stop for up to 10 days (Rattenborg et al., 2016). As many birds make non-stop flights lasting days, weeks, or months, the ability to perform adaptively with limited sleep may be common among birds (Rattenborg, 2006) and perhaps other animals that face ecological demands that require prolonged wakefulness in the wild (Siegel, 2009). Indeed, it was recently discovered that Northern elephant seals (*Mirounga angustirostris*) sleep 11 h per day on land, but only 2 h during several months spent at sea (Kendall-Bar et al., 2023). Instead of sleeping little, some animals mitigate the ecological costs of sleep by sleeping in a highly fragmented manner. The most extreme example is nesting chinstrap penguins (*Pygoscelis antarcticus*) which obtain over 11 h of sleep per day but do so via thousands of microsleeps lasting just 4 s on average (Libourel et al., 2023). By demonstrating that reduced performance is not an evolutionarily inescapable outcome of sleep loss or fragmentation—results that comport with Schmidt's energy allocation model—these field-based studies on birds and mammals inform our theories about sleep's functions.

To account for torpor and prolonged wakefulness, the energy allocation model 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 model 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.

4 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 large 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 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, it seems the ancestral pattern is to accumulate sleep in many short bouts across the day and night (Capellini et al., 2008b); 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 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., 2008b).

The longstanding view of human sleep as monophasic is not universally accepted (Ekirch, 2006). Based on analyses of historical documents, it was argued that a pattern of strictly monophasic sleep in humans is a derived character reflecting 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.

As compelling as this historical argument may be, a study of sleep in three hunter-gatherer societies in Africa and South America provided evidence 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 industrialized societies, these findings suggest that industrialization has not substantially altered human sleep habits, at least regarding total sleep time. Further, the data suggest that the bimodal pattern of sleep, recently identified from the historical record in pre-industrialized European societies, was a more recent response to life at higher latitudes and longer winter nights (Kappeler, 1998; Samson and Nunn, 2015).

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. 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 (Kappeler, 1998; Samson and Nunn, 2015).

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

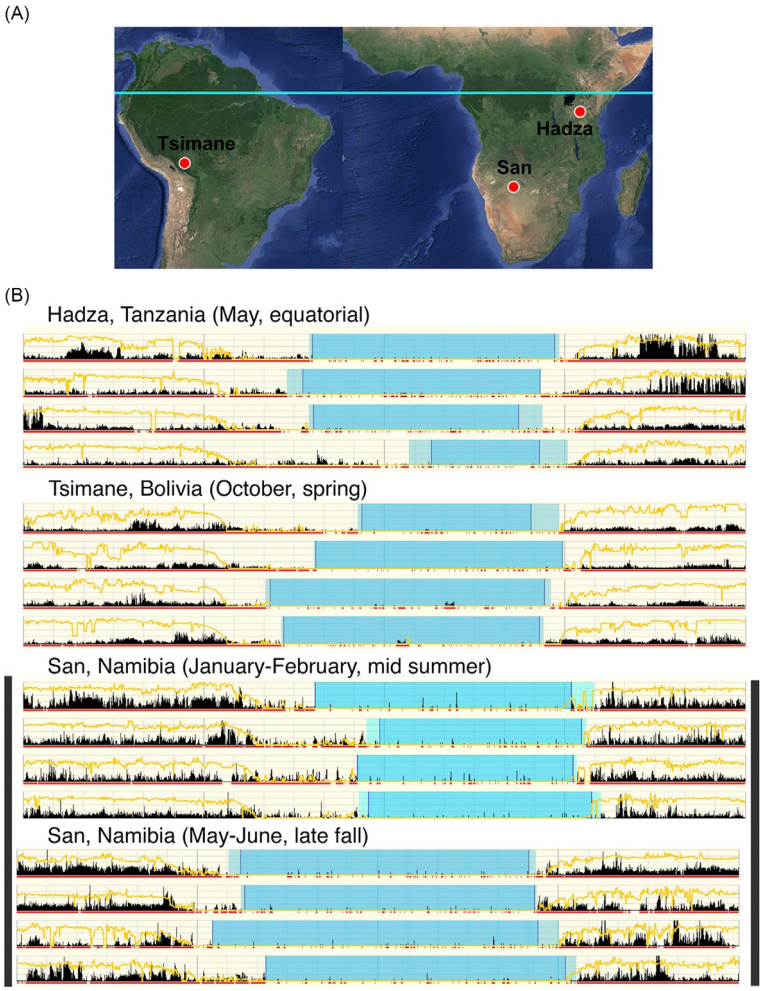

Fig. 2 Evidence of monophasic sleep from humans in three preindustrial societies. (A) Location and names of the societies. The green line shows the equator. (B) Actograms for one individual recorded across multiple days from each of the societies. The San subject was also recorded across two seasons. 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. Map lines delineate study areas and do not necessarily depict accepted national boundaries. Reprinted with permission from Yetish G, et al. (2015) Natural sleep and its seasonal variations in three pre-industrial societies. *Current Biology* 25(21): 2862–2868, Copyright 2015, Elsevier Ltd.

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 (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 (e.g., predatory carnivores, disease-carrying insects) that demanded adaptive responses. For example, for ground-sleeping hominids, the use of fire—in addition to providing warmth and fostering social interactions—would have discouraged predation and insects. Sleeping on the ground may also have placed a premium on early humans maximizing the benefits of sleeping for shorter amounts of time. Indeed, the "sleep intensity hypothesis" was proposed recently to account for why humans appear unique in concentrating such a high percentage of AS into a relatively short period of consolidated sleep (Samson and Nunn, 2015).

In summary, 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.

Fig. 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. (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. (D) Terrestrial beds are used by massive apes (male chimpanzees and gorillas) and humans. (A) Photo accredited to Manfred Eberle. (C) Photo accredited to Kathelijne Koops. (D) Photo of Hadza hunter accredited to Mathiew Paley. From Samson DR and Nunn CL (2015) Sleep intensity and the evolution of human cognition. *Evolutionary Anthropology: Issues, News, and Reviews* 24(6): 225–237, Copyright 2015, courtesy of David Samson.

5 Lessons from comparative studies of sleep

The study of sleep across animals can be viewed from several perspectives. The *model-based approach* aims to gain insight into sleep in humans by performing experiments on other animals, especially 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. Research on flies also provides an example of a *comparative-based approach*, as studies in such "simple" animals may reveal the initial or core functions that drove the evolution of sleep (Hendricks et al., 2000b). Consequently, both model- and comparative-based approaches, as applied in this context, usually focus on the similarities 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 some biological processes may be performed more effectively during sleep than wakefulness (see Section 3). 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 (or without the same types of) brain rhythms (Yap et al., 2017). Embracing and ultimately reconciling this difference will undoubtedly refine our understanding of the functions of mammalian brain rhythms. Consequently, a comparative approach yields insights into sleep that are obscured when we rely exclusively on a small number of laboratory species.

In the next section, we highlight the similarities and differences in QS and AS across taxonomic groups to further show how a comparative approach informs our understanding of the mechanisms, functions, and evolution of sleep.

5.1 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, but the patterns of brain activity are 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 (Sharon et al., 2024), several fundamental questions remain. Do mammalian rhythms play a causal role in processing memories or do they simply covary with other cellular processes that support memory? Is the frequency of a rhythm critically important or can rhythms of different frequencies perform the same function in different taxonomic groups (Ramon et al., 2012; Voirin et al., 2014)? Do all sleep rhythms have a function or are some rhythms epiphenomena that merely reflect the structure of the neuroanatomical circuits that underlie them? 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 post-sleep performance (Fig. 4; Dudai et al., 2015). 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, wake-related information from higher-order neocortical association areas 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 (Dudai et al., 2015; Staresina et al., 2015; Lopez et al., 2024). Specifically, during QS, the slow oscillation coordinates the timing of thalamocortical sleep spindles (intermittent 12–15 Hz oscillations) and hippocampal sharp-wave ripples (SWRs) such that they co-occur during the up-state of the slow oscillation (Steriade, 2006). SWRs are highly synchronous bursts of activity during which neuronal sequences activated during wakefulness are replayed in the hippocampus and in the neocortex in a coordinated manner in conjunction with sleep spindles (Buzsáki, 2015). Cortical spindles are thought to create conditions conducive to the strengthening of the cortical memory that is replayed. Over time, this process can lead to the transfer of memories from the hippocampus to the neocortex where they are integrated with pre-existing memories for long-term storage.

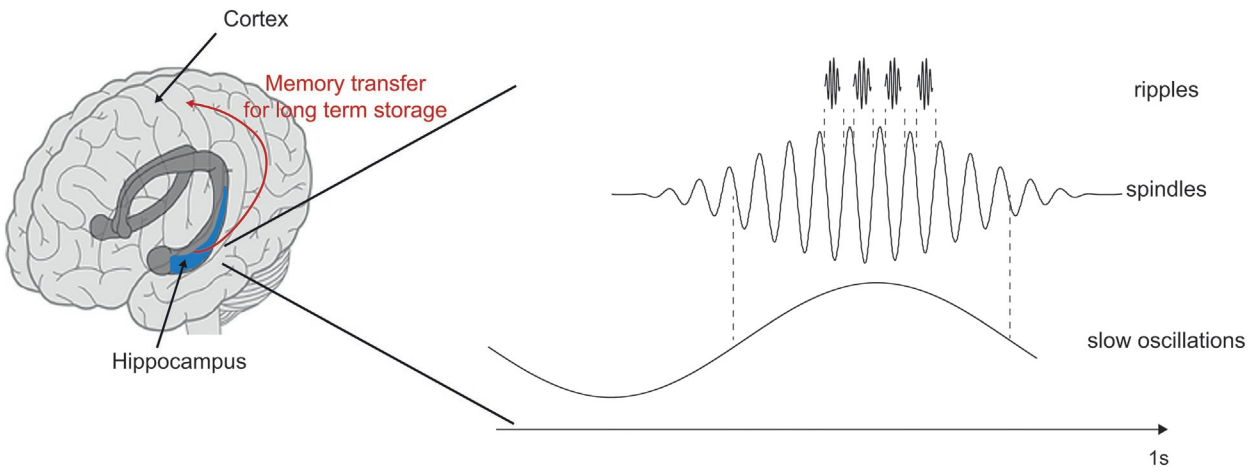

Fig. 4 Sleep-related brain rhythms implicated in transferring hippocampal memories to the neocortex for long-term storage and integration with preexisting memories. Neocortical slow oscillations influence the timing of hippocampal sharp-wave ripples (SWRs; only the ripple component is shown) and thalamocortical sleep 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.

Birds provide a particularly informative comparison with mammals, as many, but 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 can perform 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). Despite these similarities between mammals and birds, there are major differences in hippocampal neuroanatomy (Rattenborg et al., 2011; Rattenborg and Martinez-Gonzalez, 2013). In contrast to the mammalian hippocampus that is reciprocally connected with regions throughout most of the neocortex, the avian hippocampus receives only olfactory and visual cortical input (Shanahan et al., 2013). Moreover, there is no solid evidence for the mammalian-like transfer of information out of the avian hippocampus. Collectively, these findings indicate that the scope of information reaching the hippocampus and the way it is subsequently processed differ 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 wake-like activated EEG pattern. Also, as in mammals, slow waves propagate through the avian brain as traveling waves (van der Meij et al., 2019). However, sleep spindles (which are closely linked with slow waves in mammals) have not been detected in birds during QS (van der Meij et al., 2019). Although hippocampal SWRs were not found in pigeons (Rattenborg et al., 2011), they were recently reported in sleeping songbirds (Payne et al., 2021), though it is not known whether they play a role in transferring hippocampal memories in these species. The apparent absence of spindles, a proposed component of SWR-mediated hippocampal memory transfer in mammals, suggests that avian SWR might simply process memories locally within the hippocampus. 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 sharpen our understanding of mammalian sleep.

What might be the general function of slow waves shared by birds and mammals? One clue relates to 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., 2011b). 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 waves may be involved in processing information locally via memory reactivation (Chauvette et al., 2012) or synaptic homeostasis (Huber et al., 2004).

Despite differences from mammals in their hippocampal system, birds depend on sleep-dependent memory consolidation for several different forms of learning, including 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 result with finches is of particular interest because they are 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, with the quality of the song degrading during nightly sleep and improving with waking practice during the day (Deregnaucourt et al., 2005; Shank and Margoliash, 2009). Over a longer timescale, however, another 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 current understanding.

The discovery of unihemispheric QS in marine mammals and birds seems to have 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 can 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 (*Callorhinus ursinus*) switch from sleeping bihemispherically on land to sleeping unihemispherically in the water (Lyamin et al., 2018). Although this sleep pattern facilitates keeping the nostrils above the surface, it may also serve an anti-predator function, as seals keep the open eye facing down into the water, perhaps to detect approaching sharks (Kendall-Bar et al., 2019).

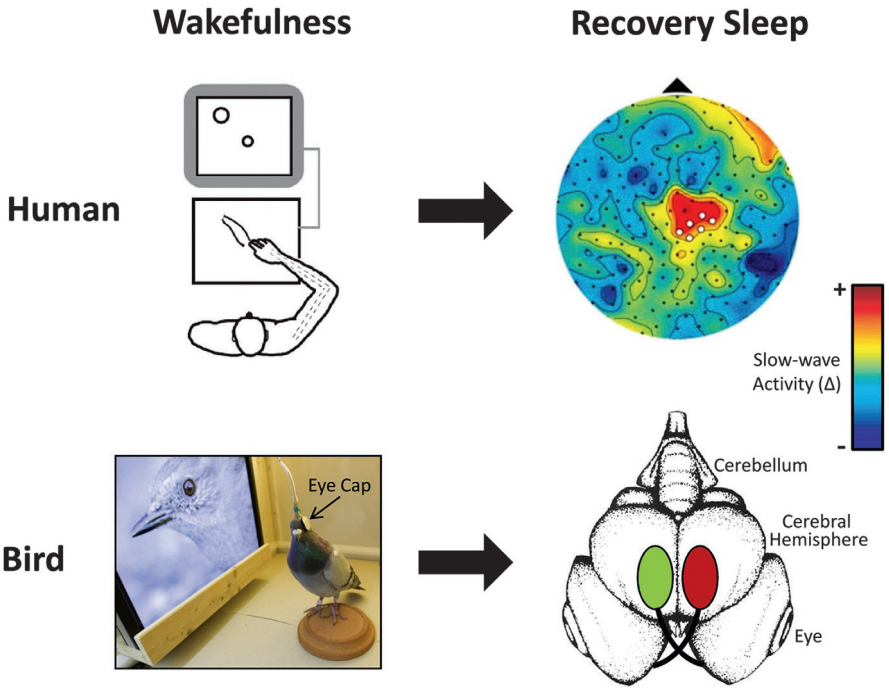

Fig. 5 Local use-dependent regulation of electroencephalogram (EEG) slow-wave activity (SWA) in humans and pigeons during quiet sleep. In humans, high-density EEG recordings show a local increase in SWA, a measure of sleep intensity, in the right parietal neocortex during QS following performance of a visuomotor task. Colors depict local increases (dark red) and decreases (dark blue) in SWA from baseline. 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 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 NC, Lima SL, and Lesku JA (2012) Sleep locally, act globally. *Neuroscientist* 18(5): 533–546, Copyright 2012, Sage Publications.

Based on these findings in ducks and fur seals, researchers asked whether a similar process might explain why people sleep poorly on their first night in a new environment (Tamaki et al., 2016). Remarkably, on the first night only, the left hemisphere showed lower slow-wave (or delta) activity during QS and was more responsive to auditory stimuli than the right hemisphere. In addition, individuals with greater interhemispheric asymmetry took longer to fall asleep. Collectively, these findings suggest 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 4). This study further illustrates 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 non-avian reptiles, amphibians, and fish. Although sleep in fish and amphibians remains poorly studied, especially at the electrophysiological level (but see below), several reptilian species have been examined. However, 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; Rattenborg, 2007; Libourel and Herrel, 2016). Although some of this diversity may reflect genuine interspecific differences, in some cases, markedly dissimilar results are reported by different labs studying the same species. Such inconsistent findings suggest that the characterization of sleep in non-avian reptiles is more sensitive to recording methods and experimental conditions (e.g., ambient temperature) than in mammals and birds. Lacking a current resolution of these issues, the following scenario for the evolution of QS-related slow waves is proposed tentatively.

Despite discrepancies, several studies report consistent findings in non-avian 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 (a) have a similar morphology and duration, (b) increase after sleep deprivation, and (c) 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). Infrequent bursts of neuronal activity have also been reported across the telencephalon of sleeping zebrafish larvae using calcium imaging (Leung et al., 2019). 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, their functions may be more pronounced in mammals and birds, perhaps contributing to the maintenance of their large brains with high neuronal density and complex cognitive abilities. Further, 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), perhaps reflecting a trade-off between memory reactivation and cellular rest, with mammals and birds investing more in the former at the expense of the latter.

Although insects are distantly related to the vertebrates discussed above, important similarities and differences exist that also inform our understanding of mammalian sleep. Kaiser and Steiner-Kaiser were the first to describe changes in central nervous system activity during sleep in an invertebrate (Kaiser and Steiner-Kaiser, 1983). 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 (LFP) recordings from the optic lobe in flies showed a reduction in power across a broad range of frequencies (van Alphen et al., 2013). Similarly, calcium imaging of the mushroom bodies showed that neurons become quiet during sleep in flies (Bushey et al., 2015); however, recordings of the central brain revealed a 7–10 Hz oscillation during transitions to and from sleep (Yap et al., 2017). Although the decreased neuronal activity observed in deeply sleeping 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.

In flies, sleep is implicated in learning-related processes such as synaptic homeostasis (Donlea et al., 2009; Gilestro et al., 2009) and memory consolidation (Donlea et al., 2011) that, in mammals, are thought to depend on specific brain rhythms. That these functions occur in flies without those brain rhythms indicates that there is still much to learn about the mechanisms underlying sleep-dependent plasticity. This example also illustrates how a deeper understanding of the differences between taxa in sleep-dependent plasticity could lead to novel insights into the mechanisms and functions of mammalian sleep.

5.2 Active sleep

As with 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 linked with the fundamental functions of this state.

The architecture of avian AS bears many similarities to mammalian AS, as well as some potentially informative differences. As in mammals, in some (but not all) avian species, the number and duration of AS episodes increases over the night (Szymczak et al., 1996; Martinez-Gonzalez et al., 2008; Low et al., 2008). Moreover, in pigeons, the amount of AS increases after short- and long-term sleep deprivation (Tobler and Borbély, 1988; Martinez-Gonzalez et al., 2008; Newman et al., 2009). Despite these similarities, and in contrast to mammals, individual episodes of AS tend to be very short in birds, usually not lasting more than 10 s (Fig. 6). (The short duration of AS episodes does not appear to be an adaptation to protect them from falling out of trees, as AS 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 6.1), birds can have hundreds of AS episodes each day, indicating that either the functions of AS in birds are realized within relatively short time intervals, or that entry into AS initiates processes (i.e., gene expression) that have carryover effects that extend beyond each individual episode of AS. Finally, rather than exhibiting a sleep cycle consisting of one bout of QS and AS, birds, such as budgerigar parakeets (*Melopsittacus undulatus*), cycle every 30 min between periods of sleep predominated by QS and periods with frequent short bouts of AS (Canavan and Margoliash, 2020).

Despite the brevity of avian AS episodes, each bout is marked by a significant surge in cerebral blood flow (Ungurean et al., 2023) and an increase in brain temperature (Ungurean et al., 2020), similar to what is observed in mammals. The increase in brain temperature likely results from the inflow of warmer blood from the body's core to the brain to support neuronal activity in brain areas active during this state. As shown using functional magnetic resonance imaging (fMRI; Fig. 7), the areas with the greatest metabolic activation during avian AS significantly overlap with those previously described in mammals, and include visual and limbic networks, the avian prefrontal-like area, and associative sensory regions. These observations suggest that AS functions that are linked to visual and sensory activity are conserved across these taxa. Interestingly, the increased cerebral blood flow during AS was also associated with decreased ventricular cerebrospinal fluid (CSF) flow. By contrast, in both birds and mammals, the highest CSF flow occurs in QS, which has been associated with increased clearance of metabolic waste from the brain via the recently described glymphatic system (Rasmussen et al., 2022). Thus, those functions of AS that are dependent on increased neuronal activity and high blood flow may come at the expense of brain clearance. However, it is possible that the transient blood-flow surges during AS can still facilitate clearance by exerting mechanical pressure in the perivascular space and forcing CSF into the parenchyma. If true, birds may capitalize on this function by exhibiting numerous brief AS episodes, potentially as an adaptation to meet the clearance needs of their neuron-dense brains (Ungurean et al., 2023).

Features of AS commonly identified in laboratory mammals include EEG activation, a hippocampal theta rhythm, muscle atonia, twitching (of which rapid eye movements, REMs, are one expression; Chase and Morales, 1983; Seelke et al., 2005), 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 above. Consequently, the hippocampal theta rhythm is not a necessary component of AS. As another example, moles and owls exhibit AS but lack rapid eye movements. In moles, this

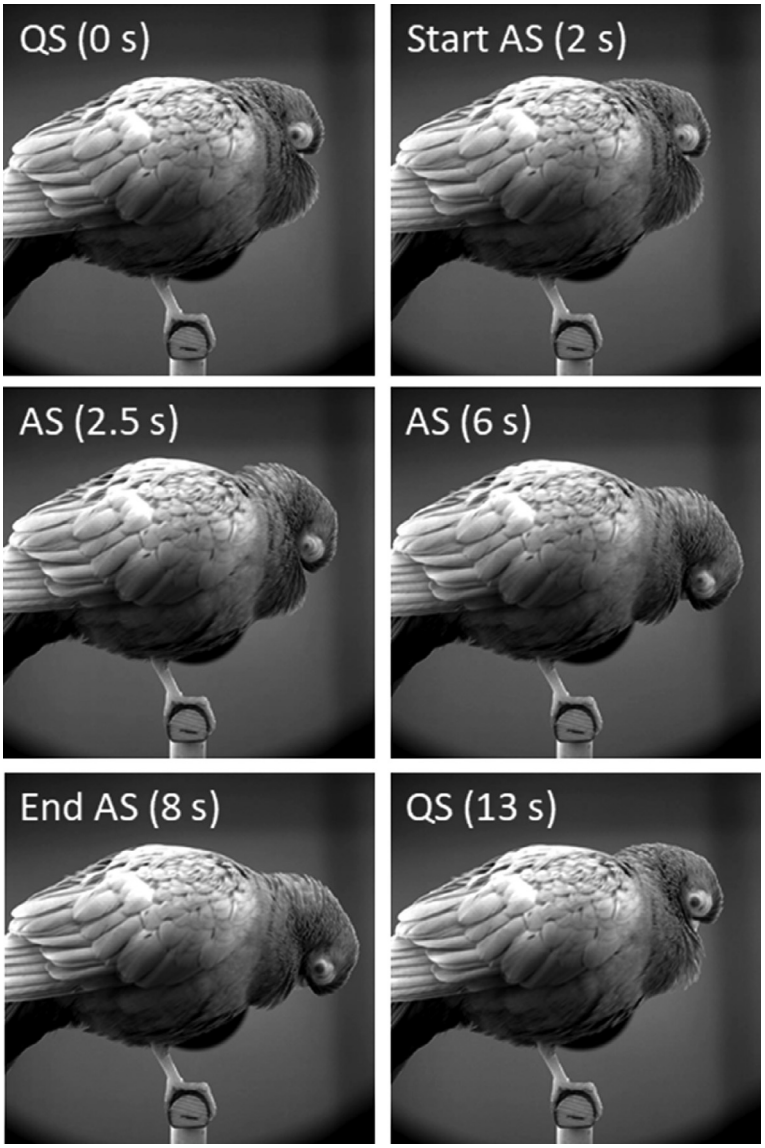

Fig. 6 Sleep behavior in a pigeon. The video frames show a domestic "Budapest" pigeon switching between quiet sleep (QS) and active sleep (AS). In the first frame (0 s), the pigeon is in QS with its dilated pupil visible through the closed eyelid (which is transparent in this variety of pigeon). The second frame shows the start of an episode of AS characterized by constriction of the pupil and a drop of the head (2.5 and 6 s), resulting from reduced tone in the neck muscles. The episode ends with dilation of the pupil (8 s) and raising of the head (13 s). The bird was balanced on one foot throughout QS and AS. Images from video recorded by Gianina Ungurean.

absence reflects their regressed visual system (Allison and Twyver, 1970b), 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. 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 by muscular mechanisms, rather than vascular mechanisms as in other mammals (Affanni et al., 2001). Collectively, these examples illustrate how comparing AS across species can help identify those components that are fundamental—mechanistically or functionally—to this state.

Some features of AS can manifest in entirely opposite ways across species, potentially reflecting different functions. One notable example is state-dependent changes in pupil size. In mammals, pupils typically dilate during aroused wakefulness, likely to enhance visual processing, and constrict during drowsiness and QS, potentially to protect sleep by limiting the amount of light reaching the retina (Yüzgeç et al., 2018). During AS in mammals, the pupil remains constricted or slowly partially dilates. In birds, however, pupil behavior follows a starkly contrasting pattern: pupils constrict during aroused wakefulness, remain dilated during QS, and rapidly constrict from this dilated state during AS (Fig. 8; Ungurean et al., 2021). This finding suggests that the protective function of pupil constriction seen in mammals may not apply to birds. Moreover, avian pupils are controlled by striated muscles, unlike the smooth muscle control in mammals, allowing for rapid and possibly voluntary constrictions during arousal and social behaviors,

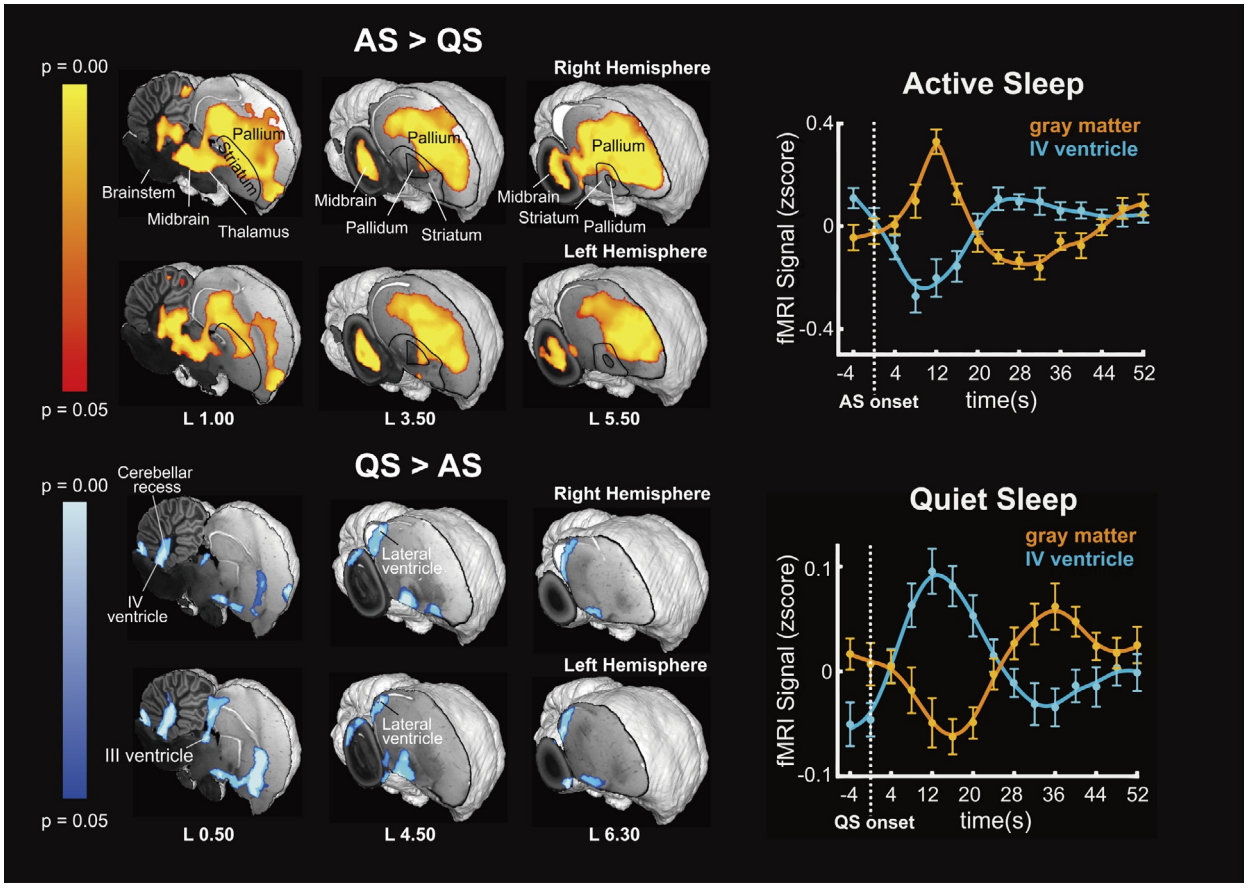

Fig. 7 Functional brain imaging in sleeping pigeons. Top left: Brain regions with significantly greater blood-oxygen-level-dependent (BOLD) signals in active sleep (AS) than quiet sleep (QS). The sagittal slices through the right and left hemispheres show increased BOLD signals throughout much of the midbrain, thalamus, striatum, and pallium, and portions of the cerebellum. Bottom left: In contrast, areas with greater signals during QS than AS were located mostly in the ventricles, perhaps reflecting increased flow of cerebrospinal fluid (CSF) within the ventricular system. The time course of the inverse relationship between gray matter BOLD signal and IV ventricle signal is shown during the onset of AS (top right) and QS (bottom right). L, distance of sagittal slice from the midline in mm. Statistically significant differences in the fMRI signals are shown on a red-yellow scale for AS > QS and a dark-light blue scale for QS > AS. The sagittal views of the left hemisphere have been mirrored to facilitate inter-hemispheric comparison. Adapted from Ungurean G, et al. (2023) Wide-spread brain activation and reduced CSF flow during avian REM sleep. *Nature Communications* 14: 3259, Copyright 2023 by the authors.

such as courtship and aggression. Thus, rapid pupil constrictions during AS could reflect memory-consolidation processes through the reactivation of brain areas involved in social interactions, including those controlling pupil size. Alternatively, these brief and rapid constrictions might reflect a form of twitching, similar to other striated muscle twitches during AS, playing a role in sensorimotor mapping and maintenance (see Section 6.3). Either way, this example highlights how the features of AS can be expressed in opposite ways across species and be linked to different sleep functions.

Reduced muscle tone 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. When horses are reluctant to lie down, the resulting REM sleep deprivation causes them to enter REM sleep while standing, leading to injurious falls (Aleman et al., 2008). The fact that they still engage in AS despite this risk of predation or falling 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 (e.g., cortical activation) can occur without atonia.

Marine mammals also experience reduced muscle tone during AS, even though it can interfere with breathing (Lyamin et al., 2018). Although sea otters (*Enhydra lutris*) 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. 9; Lyamin and Oleksenko, 2000). Similarly, fur seals (family Otariidae) keep their nostrils above the surface by floating on their side while paddling with 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 (Lyamin et al., 2018). Rather than reducing the time spent in AS, true seals (Kendall-Bar et al., 2023) and manatees (Lyamin and Siegel, 2019) solve this problem by simply holding their breath during AS.

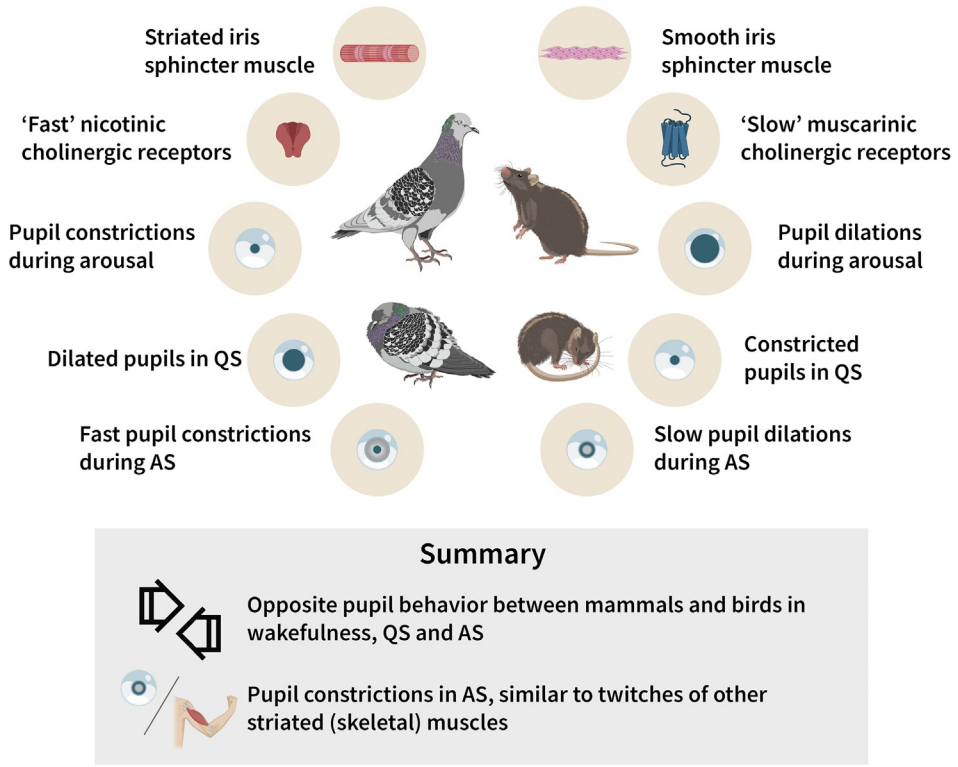

Fig. 8 Differences in the pupillary behavior of mammals and birds during wakefulness, quiet sleep (QS), and active sleep (AS), illustrating how the anatomy and physiology of a taxonomic group can dramatically influence the expression of sleep-related phenotypes. The iris sphincter muscle consists of slow, smooth muscles in mammals and fast, striated muscles in birds. Illustrations of the pigeons and mice by Damond Kyllo. Used with permission from Rattenborg NC and Ungurean G (2022) The evolution and diversification of sleep. *Trends in Ecology and Evolution* 38: 156–170, Copyright 2022, Elsevier, Inc.

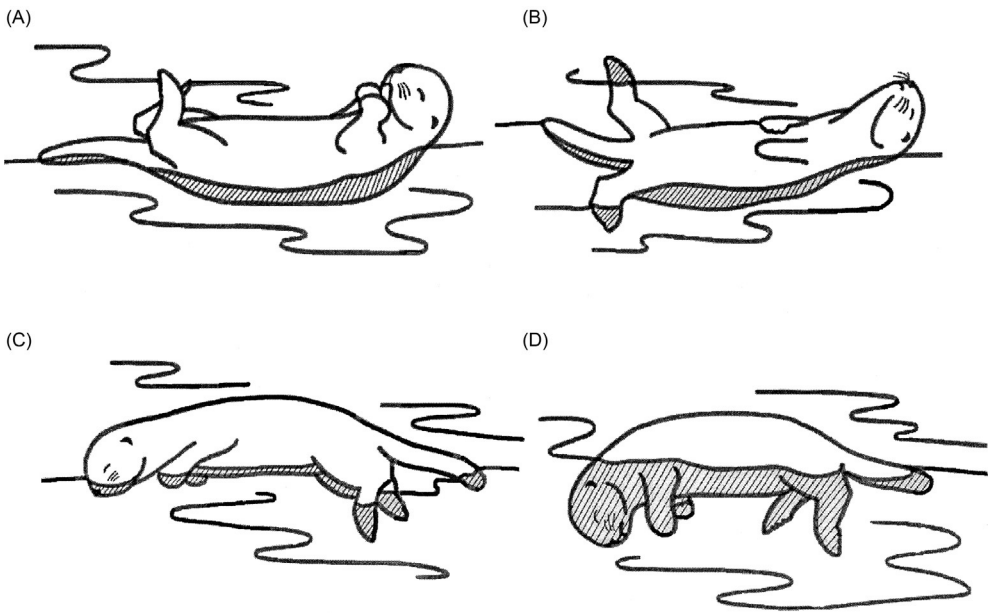

Fig. 9 Typical sleep postures of sea otters sleeping in the water. (A) During quiet sleep (QS), sea otters float on their back with their head and limbs held out of the water. (B and C) During the transition from QS to active sleep (AS), a loss of muscle tone causes the head and limbs to drop and the otter to roll over. (D) During AS the otter floats on its belly with the nostrils below the surface. Reprinted with permission from Lyamin OI and Oleksenko AI (2000) Behavioral sleep in captive sea otters. *Aquatic Mammals* 26: 132–136, Copyright 2000, Aquatic Mammals.

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, twitching has been observed, albeit infrequently, 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 (Fig. 6). QS can occur with one (e.g., ducks; Rattenborg et al., 1999, 2000) or both (e.g., ostriches and owls) eyes open (Lesku et al., 2011a), 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 thermoregulatory behaviors (e.g., shivering and panting) during avian AS (Graf et al., 1987; Scriba et al., 2013a). Despite behavioral signs of reduced muscle tone in birds, nuchal EMG recordings rarely show signs of atonia. In geese, muscle tone appears to be maintained actively during AS depending on how the head is supported (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. 10). As observed in other birds when the head is not supported during sleep, it can droop slowly over time. More generally, muscle control during sleep appears to be regionally specific, as muscle groups controlling various body parts (head, wings, feathers) can show differential signs of reduced tone (Rattenborg, personal observation). Also, in birds that sleep while standing on one foot with the other foot held off the ground (e.g., 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 twitching and reduced muscle tone 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). 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 (e.g., 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 brainstem neuronal activity showed an irregular pattern during AS like that observed in placental mammals. This finding suggested that the ancestral sleep state for mammals consisted of cortical slow waves occurring in conjunction with AS-like activity in the brainstem. In contrast, Nicol et al. (2000) reported EEG activation accompanied by REMs in 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, during AS, the platypus EEG usually showed slow waves characteristic of QS in therian mammals.

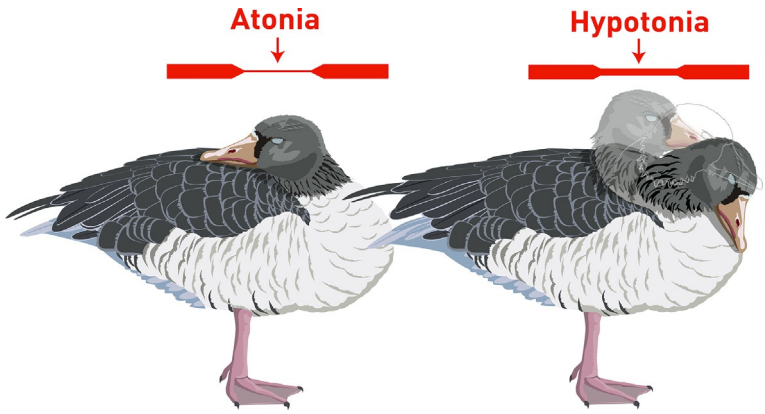

Fig. 10 Behavioral control of muscle tone during active sleep (AS) in geese. Geese can sleep with their head supported on their back (back sleep) or with their head unsupported, facing forward (front sleep). During back sleep, mammalian-like muscle atonia is observed in the neck electromyogram, whereas 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. Illustrations by Damond Kyllo. Adapted in part from Dewasmes G, et al. (1985) Polygraphic and behavioral study of sleep in geese: Existence of nuchal atonia during paradoxical sleep. *Physiology & Behavior* 35: 67–73.

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.

The few studies of Palaeognathic birds revealed a mixed platypus-like sleep state in ostriches (Lesku et al., 2011a; Lyamin et al., 2020), but not in another member of this group (Tisdale et al., 2017). During QS, adult 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 like that observed during AS in other birds, most of the other features of AS 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. By contrast, a study of elegant crested tinamous (*Eudromia elegans*)—small, flying Palaeognathic birds that most closely resemble the ancestral condition for this group—exhibit well-defined sleep states like those of Neognathic birds (Tisdale et al., 2017). Thus, the mixed sleep state observed in ostriches does not appear to reflect the ancestral sleep patterns of early birds. Why ostriches sleep like platypuses remains a mystery.

The similarities between mammalian and avian AS suggest that these states were present in their common amniote ancestor or evolved independently in each lineage. Evidence of AS in non-avian reptiles would support the common-ancestry scenario. Recent studies revealed two sleep states in a lizard, bearded dragons (*Pogona vitticeps*), that exhibit QS- and AS-like properties. AS-like sleep in dragons was primarily characterized by wake-like brain activity and eye movements (Shein-Idelson et al., 2016; Libourel et al., 2018). Interestingly, QS and AS cycling occurred with precise ~80-s periods, with equal time spent in each state. Also, unlike mammalian and avian AS, the duration of AS did not lengthen across the night. Remarkably, light pulses delivered at night could advance or delay the next bout of AS in a phase-dependent manner (Fenk et al., 2024). Also, the period of the cycle could be shortened or lengthened through entrainment to shorter or longer light pulse intervals, a mechanism not known to control the QS/AS cycle in mammals and birds. The cyclic nature of the dragon sleep state oscillation is reminiscent of an infraslow oscillation occurring during QS in mammals characterized by cycles in norepinephrine, sleep-spindle activity, eye movements, and micro-arousals (Yüzgeç et al., 2018; Kjaerby et al., 2022; Osorio-Forero et al., 2024). Determining whether these findings reflect a QS/AS cycle or an infraslow oscillation during QS will have important implications for understanding the evolution of sleep states in amniotes.

Fish provide an even earlier window into the evolution of sleep states in vertebrates. A study using calcium imaging of restrained young zebrafish revealed two sleep states (Leung et al., 2019). The QS-like state was characterized by bursts of activity in the telencephalon that became more synchronous after sleep deprivation. The AS-like state started with a bilateral contraction of the trunk muscles that propagated toward the tail. This movement pattern was followed by a widespread wave of neuronal activity that propagated from the base of the brain to the forebrain. This wave of activity was followed by suppressed neuronal activity for 20 min, a response never observed following AS in mammals and birds. Also, although zebrafish can move their eyes during wakefulness, they did not move them during the AS-like state.

A subsequent calcium imaging study of unrestrained young zebrafish also reported QS- and AS-like states, but with very different features (Choudhary et al., 2023). QS occurred primarily at night, whereas AS occurred during the day immediately after bouts of wakefulness. AS was characterized by highly rhythmic saccades, listing of the body, increased arousal thresholds, and a widespread reduction in brain activity relative to wakefulness. Notably, locus coeruleus activity was reduced during this state, as it is during mammalian AS. In addition to the stark differences between the sleep states described in restrained and unrestrained zebrafish, the occurrence of the AS-like state during the day after periods of wakefulness and the regularity with which the eyes move to the left and right are unlike mammalian and avian AS, which follow periods of QS and are associated with irregular eye movements. Clearly, more studies are needed to resolve the nature of sleep states in fish and their relations with QS and AS in mammals and birds.

Recent studies of cephalopods (cuttlefish and octopuses) suggest that an AS-like state evolved independently in this taxonomic group. Cephalopods are members of the phylum Mollusca, which also includes gastropods (snails). Sleep has been investigated in a few species of gastropods and cephalopods. The closest relative to Mollusca examined for sleep are flatworms. Behaviorally, flatworms and gastropods exhibit QS, but no signs of AS have been detected (Stephenson and Lewis, 2011; Vorster et al., 2014; Omond et al., 2017). By contrast, cuttlefish and octopuses exhibit distinct AS-like states, characterized by changes in skin brightness, pattern, and texture, as well as movements of the eyes, head, and tentacles (Frank et al., 2012; Iglesias et al., 2019; de Souza Medeiros et al., 2021; Pophale et al., 2023). During the QS-like state, the skin is pale and smooth, and the eyes and body are still. These episodes are followed by shorter periods of AS, characterized by rapid changes in skin brightness, pattern, and texture that resemble fragments of the patterns observed during waking behaviors. In addition, the eyes, head, and tentacles exhibit rapid movements. These body movements and changes in the skin are mediated by striated muscles, and therefore can be viewed as a type of twitch akin to those observed during mammalian and avian AS. In octopuses, arousal thresholds are elevated during both sleep states (de Souza Medeiros et al., 2021; Pophale et al., 2023). LFP recordings from the brain of octopuses did not reveal slow waves during QS, but did reveal intermittent bursts of activity resembling mammalian sleep spindles (Pophale et al., 2023). Also, AS was characterized by LFP activity resembling wakefulness. Finally, as in mammals and birds, AS deprivation caused a compensatory increase in AS (Pophale et al., 2023). Remarkably, the AS-like state in cephalopods is more like AS in mammals and birds than are the AS-like states described in more closely related lizards and fish. The apparent absence of an AS-like state in snails and flatworms suggests that this state evolved independently in cephalopods.

In addition to cephalopods, a recent study of jumping spiders (*Evarcha arcuate*) suggests that AS exists in other invertebrates (Rößler et al., 2022). Young jumping spiders spend the night hanging from a single thread of silk. Most of the time, they are

motionless. However, every 15 min the muscles keeping the spider's legs extended relax, causing the legs to curl toward the body, after which the legs and most other body parts begin to twitch. In addition, their dark retinal tubes, visible through their transparent bodies, move rapidly behind the fixed lenses of their large frontally facing eyes, even though there is nothing for them to watch. After a minute, the spiders become quiet again and the cycle repeats across the night. Although arousal thresholds and brain activity have not been assessed, it seems likely that spiders exhibiting these behaviors are asleep, as the twitching does not resemble the purposeful movements observed in awake spiders. The discovery of AS-like states in ectothermic cephalopods and jumping spiders challenges the hypothesis that the evolution of AS is linked to the evolution of endothermy.

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. Thus, rather than focusing primarily on which species or groups "have" AS or QS, it is better to place more emphasis on the evolution of the individual components that comprise them (Blumberg, 2013; Blumberg et al., 2020).

6 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 during early development. This is true in mammals (Roffwarg et al., 1966; Shimizu and Himwich, 1968; Jouvet-Mounier et al., 1970; Gramsbergen et al., 1970) as well as owls (Scriba et al., 2013a,b), zebrafish (Sorribes et al., 2013), and flies (Shaw et al., 2000; Kayser et al., 2014). In addition, in mammals and birds, AS is highest early in life and declines over development (Fig. 11; Roffwarg et al., 1966; Jouvet-Mounier et al., 1970; Scriba et al., 2013a; Lesku and Rattenborg, 2014).

It can reasonably be argued that the search for the developmental origins of sleep, in vertebrates and invertebrates, provides a surer path to revealing its phylogenetic origins (Corner and van der Togt, 2012; Corner, 2013b). 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 (i.e., not reflexive) bursts of motor activity observed in chick and rat embryos (Hamburger, 1963; Narayanan et al., 1971), were considered by Corner the direct developmental precursors of sleep.

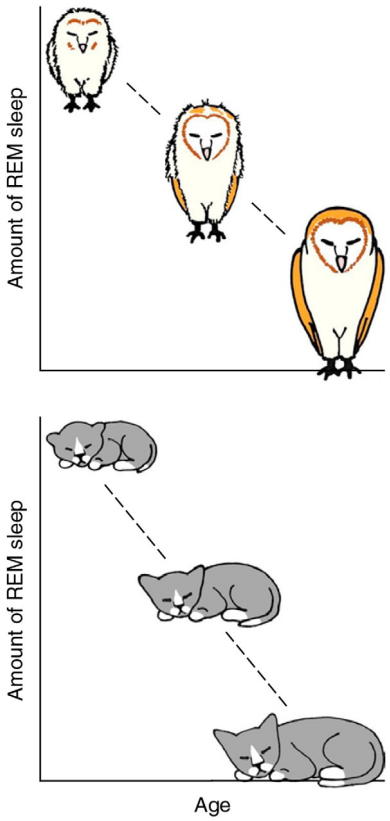

Fig. 11 Age-related decline in active (or REM) sleep in barn owls (top) and kittens (bottom). Absolute values not shown. Reprinted with permission from Lesku JA and Rattenborg NC (2014) Avian sleep. *Current Biology* 24: R12–R14, Copyright 2014, Elsevier Ltd.

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; West-Eberhard, 2003; Carroll, 2006; Blumberg, 2009; Arthur, 2011), 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 et al., 2020).

The propensity for animals to sleep more in early development demands an explanation. One approach within the comparative tradition to provide such an explanation entails associating sleep measures with physiological and life-history variables such as gestation length, longevity, metabolic rate, neonatal and adult brain weight, and risk of predation (Zepelin and Rechtschaffen, 1974; Siegel, 2005; Roth et al., 2006; Capellini et al., 2008a; Cao et al., 2020). Though much has been learned using such approaches, they have limitations for understanding developmental processes (but see Cao et al., 2020). For example, Capellini et al. (2008a) noted across a variety of species that there was no statistical association between neonatal brain weight and subsequent REM sleep durations measured in adults. Based on this lack of an association, they suggested that "the major role of REM sleep is not linked to brain development" (p. 1772 of Capellini et al., 2008a). But such a suggestion requires that one take 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 a measure such as neonatal brain weight. Consider, for example, the role that sleep plays in modulating plasticity in visual neocortex (Frank et al., 2001) or that twitching is thought to play in the activation of developing sensorimotor neural circuits (see Section 6.3). Why would one expect such processes to be associated with neonatal brain weight?

Another approach to assessing the developmental importance of sleep is to search for species that violate expectations. For example, two decades 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 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 of Lyamin et al., 2005).

Although subsequent work has questioned the dolphin findings noted above, 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.

In that regard, it is 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. Norway rats (*Rattus norvegicus*) are altricial with short gestation lengths of 21 days that nonetheless exhibit sleep-like behavior beginning approximately 4 days before birth (Narayanan et al., 1971; Robinson et al., 2000). Domestic sheep are precocial and exhibit sleep as fetuses beginning many weeks before the end of their 150-day gestation period (Karlsson et al., 2010). Cetaceans are highly precocial with long gestation lengths for mammals of their body size (Martin et al., 2005); for example, 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 caution when using comparative analyses to test specific hypotheses about the developmental 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.

6.1 Development of ultradian and circadian sleep-wake rhythms

One of the 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 very rapid sleep-wake cycling across the day and night (Fig. 12; Karlsson et al., 2004; Blumberg et al., 2005). Over the first two postnatal weeks, sleep and wake bouts consolidate as brainstem 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, reflecting the fact that rats are nocturnal and humans are diurnal (Gall et al., 2008).

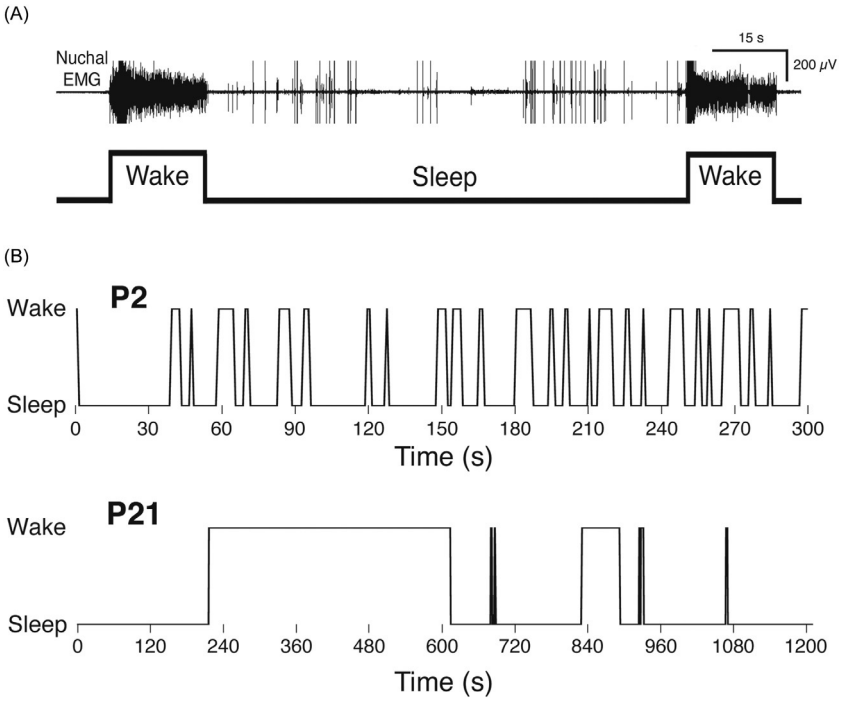

Fig. 12 Developmental changes in sleep consolidation in Norway rats. (A) Top: A 2.4-min record in a P8 rat of nuchal electromyogram (EMG) showing two brief periods of high nuchal muscle tone (indicative of wakefulness) separated by a longer period of muscle atonia (indicative of sleep). The sharp spikes 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 MS, et al. (2005) Dynamics of sleep-wake cyclicity in developing rats. *Proceedings of the National Academy of Sciences of the United States of America* 102: 14860–14864, Copyright 2005, American Psychological Association.

There are two basic levels—both 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 indicative of wake (e.g., kicking, stretching, yawning) and brief, jerky, discrete movements indicative of AS (i.e., twitches). The backdrop to these motor events is ultradian cyclicity in muscle tone (*ultradian* refers to cycles that occur more than once each day). Importantly, wake movements are produced during periods of high muscle tone and twitches are produced during periods of muscle atonia (Fig. 11). Thus, in newborn rats, these two dimensions of motor activity cohere to present organized sleep-wake states.

Focusing on muscle tone alone, we can discern another level of structure. Specifically, when we precisely measure the duration of many sleep and wake bouts and examine their statistical distributions across age, we find that sleep bouts of pups at the earliest ages distribute randomly (i.e., they follow a Poisson distribution), as do wake bouts (Fig. 13; Blumberg et al., 2005; Gall et al., 2008). 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 transforms into a power-law distribution characterized by a small proportion of exceedingly long wake bouts. Importantly, sleep bouts do not undergo this power-law transformation but rather continue to exhibit a Poisson distribution. 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 provide 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 most 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 likely targets of evolutionary modifications to sleep and wake states*.

The development of sleep and wake bouts has been investigated most extensively in rodents, including Norway rats (Blumberg et al., 2005; Gall et al., 2008), wild-type and orexin knockout 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 brainstem 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 brainstem alone, neural circuits that are sufficient to produce integrated sleep-wake cycles, inconsistent with the hypothesis that the fundamental sleep-wake "flip-flop" necessarily spans brainstem and hypothalamic circuits (Saper et al., 2001).

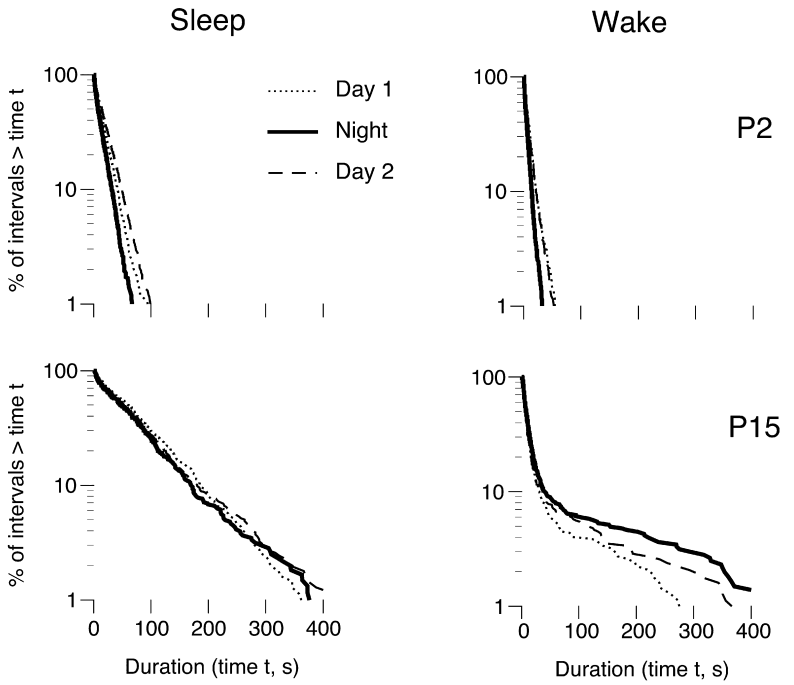

Fig. 13 Log-survivor plots of bout durations during sleep (left column) and wake (right column) for nocturnal Norway rats at P2 and P15. Pups were recorded during the day (dotted line), the subsequent night (solid line), and the next day (dashed line). Straight lines on semilog plots indicate that the data follow an exponential (Poisson) distribution. Adapted from Gall AJ, et al. (2008) The development of day–night differences in sleep and wakefulness in Norway rats and the effect of bilateral enucleation. *Journal of Biological Rhythms* 23: 232–241, Copyright 2008, Sage Publications.

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, the structure of sleep and wake bouts can be manipulated independently; 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 without affecting sleep bouts (Gall et al., 2009). Computational models of the infant sleep-wake oscillatory system, based on relatively simple networks of mutually inhibitory neurons, can 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 for 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 become longer at night (Fig. 13). 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 the nocturnal and diurnal mammals studied thus far, the SCN cannot be responsible for nocturnality and diurnality. Therefore, focus was placed instead on the retinohypothalamic tract (RHT) and the interactions between the SCN and its close functional neighbor, the ventral subparaventricular zone (vSPVZ). First, very similar developmental patterns were found in sleep and wake bouts in the two species until the end of the second postnatal week, when wake bouts diverged in the two species such that they were longer at night in the Norway rats and longer during the day in the Nile grass rats (Fig. 14). Around the same time when this behavioral change occurred, 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 anti-phase activity profiles in the grass rats. These in-phase and anti-phase activity profiles in SCN and vSPVZ were related to differential development of RHT connectivity to the two structures. Finally, a literature survey of 14 mammalian species revealed distinct patterns of RHT-to-vSPVZ connectivity that may help to explain species differences in nocturnality and diurnality.

Based on these comparative observations, it was 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 natural selection.

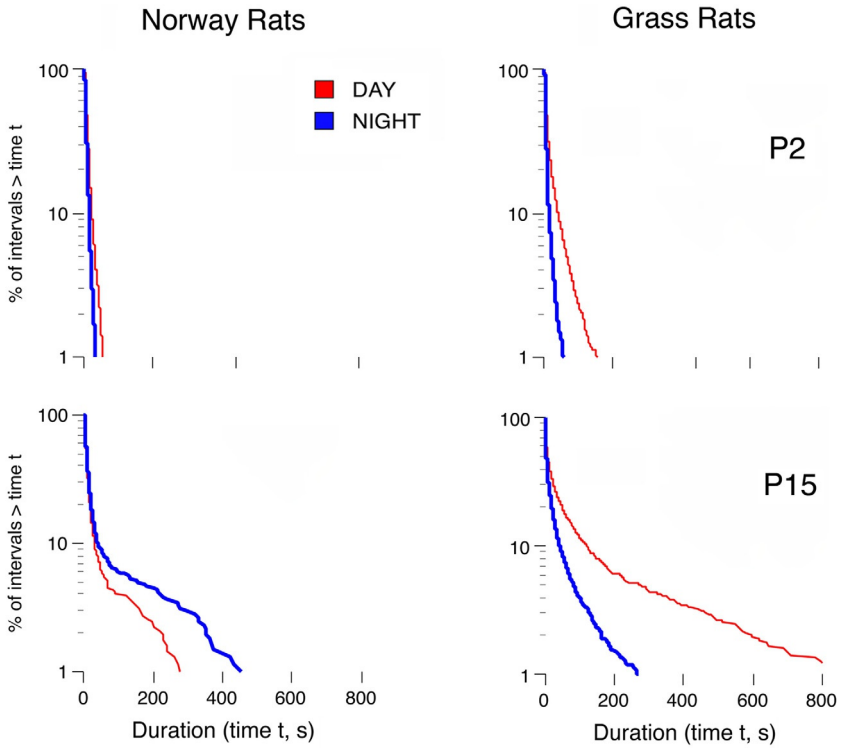

Fig. 14 Log-survivor plots of wake-bout durations in nocturnal Norway rats (left column) and diurnal Nile grass rats (right column). Data are shown for pups recorded during the day (red) and night (blue) at P2 and P15. Adapted from Todd WD, et al. (2012) Distinct retinohypothalamic innervation patterns predict the developmental emergence of species-typical circadian phase preference in nocturnal Norway rats and diurnal Nile grass rats. *Journal of Comparative Neurology* 520: 3277–3292, Copyright 2012, John Wiley and Sons.

6.2 Developmental emergence of QS and the cortical delta rhythm

As discussed in Section 5.1, the cortical delta rhythm is a defining feature of QS in adult mammals and birds. Moreover, cortical delta provides the foundation upon which many theories of sleep function have been built, including those that focus on memory consolidation (Diekelmann and Born, 2010). Cortical delta provides a metric—delta power—that is commonly used to assess the intensity of rebound sleep and its dissipation over the post-deprivation period (Rechtschaffen et al., 1999; Borbély et al., 2016).

In adult mammals, cortical delta arises from complex interactions between thalamic and cortical circuits (Steriade, 2006). However, in young mammals, the delta rhythm emerges relatively late. In rats, for example, it is only weakly detectable at P11 and gains steadily in power thereafter (Frank and Heller, 1997a; Seelke and Blumberg, 2008). Consequently, the detection of QS before P11 cannot rely on the occurrence of the delta rhythm, but rather on the other behavioral and electrophysiological components that precede delta's emergence (Blumberg and Seelke, 2010).

Does the onset of cortical delta involve a substantial reorganization of sleep structure, or a more orderly process of incorporating a new sleep component? To answer this question, recall that in rats during the first postnatal week, there are rapid transitions between periods of high muscle tone accompanied by coordinated wake movements, and periods of atonia accompanied by twitches. Moreover, interposed between periods of wake movements and twitches are periods of behavioral quiescence against a background of low muscle tone or atonia (Fig. 15). In other words, during a typical sleep-wake cycle at this age, quiet wakefulness transitions to quiet sleep. Then, at P11 as the nascent delta rhythm emerges, it fits into the QS "slot" identified at earlier ages as the period between quiet wake and AS (Seelke and Blumberg, 2008). Thus, the developmental emergence of cortical delta reflects the orderly insertion of a new sleep component, not a fundamental reorganization of sleep structure.

Nonetheless, the developmental onset of cortical delta in rats is a harbinger of QS's emergence as the predominant sleep state. Between P11 and P20 as delta power increases, the amount of time spent in QS doubles as the time spent in AS is cut by a third (Frank and Heller, 1997b). Whereas the emergence of cortical delta likely reflects (at least in part) developmental changes in thalamocortical circuits (Crunelli et al., 2018; Adamantidis et al., 2019; Uygun and Basheer, 2022), the increasing dominance of QS may reflect changes in the neural circuits that control that state. The identification of the parafacial zone (PZ)—a region in the medulla that lies dorsal to the facial nerve and ventral to the parabrachial nucleus—as a key structure regulating QS in adult mice (Anaclet et al., 2012, 2014).

The discovery of the PZ as a brainstem structure regulating QS inspired the hypothesis that developmental changes in PZ activity underlie the developmental emergence of delta-rich QS (Ahmad et al., 2024). To test this hypothesis, neural activity in the PZ was recorded in rat pups between P8 and P12 as QS-dependent cortical delta is beginning to emerge (Ahmad et al., 2024). The initial

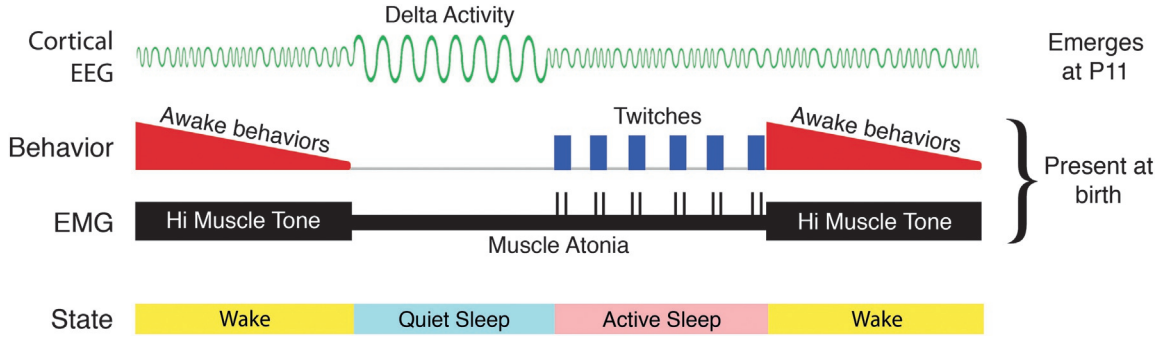

Fig. 15 Illustration of a typical sleep-wake cycle in the early postnatal period in Norway rats. Bottom row: Categories of behavioral state. Middle two rows: Electromyographic (EMG) and behaviorally observable components of the cycle. Top row: Beginning at P11, the cortical electroencephalogram (EEG) begins to exhibit the delta rhythm. Even at P11 when cortical delta is first emerging, it occurs during the period between quiet wake and active sleep as defined at earlier ages when delta is absent. Reprinted with permission from Blumberg MS, et al. (2014) The development of sleep–wake rhythms and the search for elemental circuits in the infant brain. *Behavioral Neuroscience* 128: 250–263, Copyright 2014, American Psychological Association.

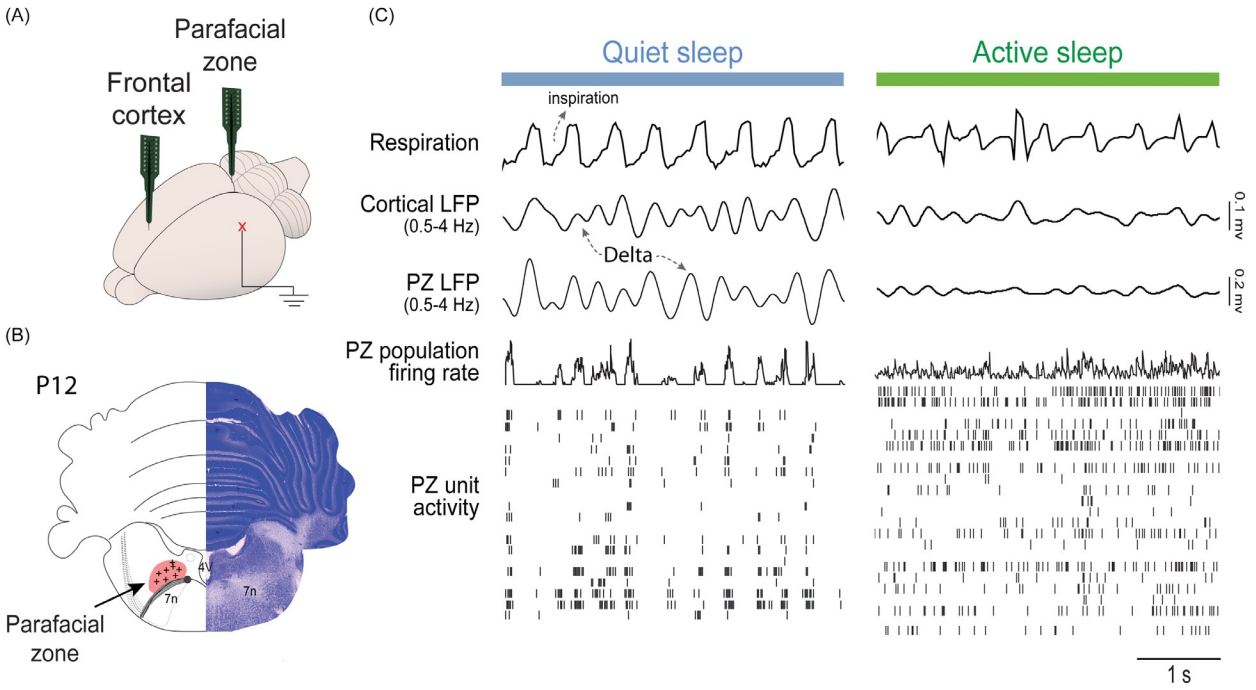

Fig. 16 Delta-rhythmic patterns of neural activity during quiet sleep in the parafacial zone (PZ) around the developmental onset of cortical delta in P12 rats. (A) Spiking and LFP activity in the PZ and frontal cortex were recorded in head-fixed pups using silicon electrodes. (B) Electrode locations within the PZ were confirmed histologically. (C) Representative recordings from a P12 rat cycling during quiet sleep (left) and active sleep (right). From top: respiration (inspiration up), cortical and PZ LFPs, PZ population firing rate, and spiking activity of individual PZ units. During quiet sleep, note the coherence of the PZ and cortical delta rhythms and the synchronization of the PZ spiking activity to the troughs of the delta rhythms. Adapted from Ahmad M, et al. (2024) Coincident development and synchronization of sleep-dependent delta in the cortex and medulla. *Current Biology* 34: 2570–2579.e5, Copyright 2024, Elsevier, Inc.

expectation was that the firing rates of PZ neurons would increase over these ages. Instead, it was the patterning of PZ activity that proved most informative: Whereas PZ neurons at P8 exhibited arrhythmic spiking activity during AS and QS, by P12 they exhibited rhythmic spiking at delta frequencies exclusively during QS (Fig. 16). Moreover, PZ's rhythmic spiking was phase-locked with a local "PZ delta rhythm" that was synchronized with cortical delta. Further, evidence that regular breathing during QS modulates PZ's rhythmic neural activity during QS suggested that a breathing-modulated circuit in the brainstem contributes to the developmental onset of PZ delta and its long-distance synchrony with cortical delta. Although it is not yet established that the PZ plays a causal role in the generation of cortical delta, these findings direct attention to the caudal brainstem as a key contributor to the developmental emergence of QS.

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 and sleep spindles, hippocampal theta, pontine waves, irregular respiration, unihemispheric sleep, penile tumescence, cessation of thermoregulation, rapid eye movements, twitching of the limbs, whiskers, pupils, and bill, and phasic activation of chromatophores in the skin. Species will differ in their 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; Blumberg et al., 2020).

6.3 Myoclonic twitching

As already noted, twitches are a prominent behavioral feature of AS. Twitches arise from activity in striated muscle, resulting in brief, jerky, and discrete movements that are easily distinguishable from the more prolonged, continuous, 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 (Blumberg and Plumeau, 2016). 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 "leak through," and it is these remnants of dreams that are observed as twitches. There are, however, reasons to doubt this perspective, not least of which is the fact that complete disconnection of the brainstem and forebrain has no discernible effect on the expression of twitching in infant rats (Kreider and Blumberg, 2000) and adult cats (Marchiafava and Pompeiano, 1964; Villablanca, 1966).

Once we set aside the epiphenomenal perspective of 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 a product with specific functions (Blumberg et al., 2013). Any functional hypothesis must account for the fact that twitches are discrete movements, that they are abundant in early development (occurring tens of thousands of times each day in infant rats), and that they can persist into adulthood. 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 lifespan in any species.

Twitches are perhaps best viewed as the sensorimotor system's version of spontaneous activity (Blumberg et al., 2022). Spontaneous activity is a robust feature of other developing sensory systems (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 (Ackman et al., 2012). In the auditory system, spontaneous activity in the cochlea plays a similar developmental role (Kersbergen and Bergles, 2024).

Twitches may be unique in that they occur exclusively during sleep, perhaps reflecting the fact that the sensorimotor system, beginning at birth in rats, uses time-sharing to balance its need to develop with its need to contribute to early wake behavior. In contrast, the visual and auditory systems do not require such time-sharing because these systems do not process light or sound, respectively, until the end of the second postnatal week. However, a lack of time-sharing in those systems does not necessarily imply that sleep-wake states do not modulate their activity in early development (Blumberg et al., 2022).

Two decades of research have revealed a wealth of twitch-related activity throughout the developing brain that reflects the unique requirements of the sensorimotor system. This activity includes brainstem-generated motor signals that produce twitches and the sensory feedback (reafference) from the twitch movements themselves that cascades throughout the brain's sensorimotor structures (Fig. 17). Altogether, this research increasingly supports the hypothesis that twitches contribute to the early development and refinement of sensorimotor maps (Blumberg et al., 2022). Moreover, this research consistently reveals another surprising feature of twitches, namely, that they are more effective than even the most vigorous wake movements at activating sensory circuits (Tiriac et al., 2014; Dooley et al., 2020), reflecting the operation of a developmentally transient mechanism in the medulla that selectively gates wake-related movements (Tiriac and Blumberg, 2016; Dooley and Blumberg, 2018).

In addition to twitch-related motor and sensory signals, there is a third class of signal that distinguishes the sensorimotor from visual and auditory modalities. This class of signal—called a corollary discharge—is produced in parallel with the motor command but does not itself drive behavior; instead, corollary discharges enable the brain to distinguish between self- and other-generated movements (Crapse and Sommer, 2008). In P8 rats, the midbrain motor structures that produce limb twitches also produce corollary discharges that are conveyed to two precerebellar structures, the inferior olive and lateral reticular nucleus (Mukherjee et al., 2018). The presence of twitch-related corollary discharge in precerebellar structures inspired the hypothesis that twitches contribute to the cerebellum's ability to compute representations—or *internal models* (Wolpert et al., 1998)—that enable accurate predictions of the sensory consequences of self-generated movements (Mukherjee et al., 2018; Dooley et al., 2021; Richardson et al., 2024).

This hypothesis was tested most directly by recording from the ventral lateral thalamic nucleus (VL; or motor thalamus), a major output of the cerebellum, during sleep and wake in P12, P16, and P20 rats (Dooley et al., 2021). At P20, but not at the two earlier ages, VL neurons exhibited activity profiles that precisely mimic the kinematic properties of a twitch—occurring *with* the movement rather than before or after it. Moreover, when cerebellar output was pharmacologically blocked, VL neurons lost their ability to mimic twitch movements. Thus, in these older pups, twitches appear well-suited to developing a cerebellar-dependent internal model of movement.

That twitches persist through the third postnatal week in rats—activating the brain and contributing functionally to the development of internal models—suggests that they continue to play functional roles into adulthood. Here, it is instructive to

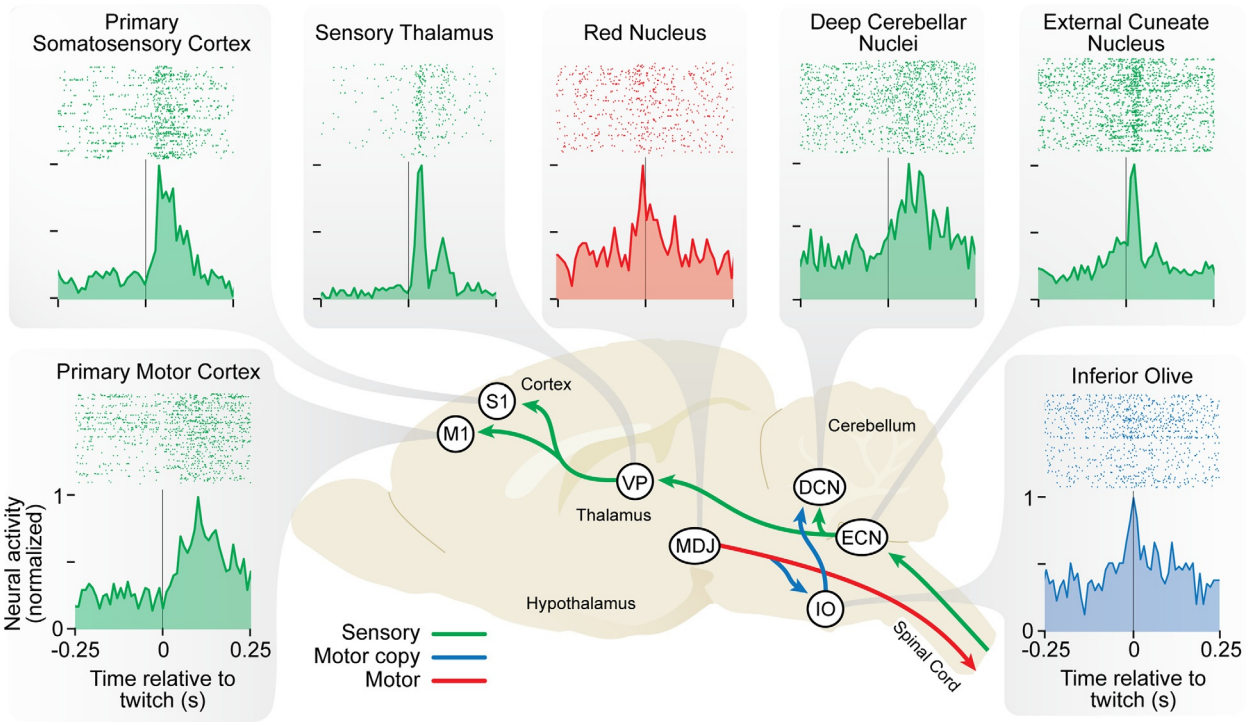

Fig. 17 Illustration of the diversity of twitch-related brain activity in week-old rats. Representative perievent histograms for a subset of those brain structures known to exhibit activity in association with forelimb twitches. The background image shows a sagittal brain section. The production of a forelimb twitch begins in the red nucleus and other brainstem motor structures within the mesodiencephalic junction (MDJ). Forelimb twitches activate proprioceptors and trigger sensory feedback (reafference) that is conveyed to the external cuneate nucleus (ECN) in the medulla, the ventral posterior nucleus (VP) in the thalamus, and primary somatosensory (S1) and motor (M1) cortices. The red nucleus and adjacent motor neurons also generate motor copies (corollary discharges) that are conveyed in sequence to the inferior olive (IO) and the deep cerebellar nuclei (DCN). Structures are color-coded based on whether they produce motor commands (red) or motor copies (blue), or whether they receive sensory feedback (green). Reprinted with permission from Blumberg MS, et al. (2022) Sleep, plasticity, and sensory neurodevelopment. *Neuron* 110: 3230–3242, Copyright 2022, Elsevier, Inc.

highlight how twitching, unlike spontaneous retinal and cochlear activity, persists into adulthood. Moreover, the parts of that body that continue to twitch in adults appear to be especially important for active sensing, that is, the directing of movable sensors—fingers, eyes, whiskers—toward objects of interest to enable more precise detection of relevant stimuli in the environment (Blumberg and Dooley, 2017). Thus, perhaps the sleep-dependent twitching of fingers, eyes, whiskers, and other effectors reflects the need to recalibrate species-specific sensorimotor systems throughout life as bodies change and new skills are learned.

Systematic comparative assessments of twitching across the lifespan are lacking. What is needed, then, are developmental-comparative analyses of twitching in which the use of species-typical sensorimotor appendages is related to the neural representations of those appendages in cortical and subcortical brain areas. Accordingly, it is predicted (for example) that digits in humans and ferrets, the multi-appendage star of star-nosed moles, the muscle-rich trunk of elephants, the bill of platypuses, 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.

7 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 (Siegel, 2009). Of course, there are gradations that lie between these two extremes: As with the waking state, there are likely many functional sleep processes that range from the universal to the near-universal to the 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 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; Lesku et al., 2012; Scriba et al., 2013a).

Sleep is a complex amalgam of components, each with its own evolutionary history. 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 (Blumberg et al., 2014). For example, the discovery in rats of PZ delta emerging alongside cortical delta around P12 introduces new opportunities for investigating the significance of rhythmic brain activity (Ahmad et al., 2024). The similarly surprising emergence of limb twitches during QS in 3-month-old human infants, and their temporal association with sleep spindles, suggests another dimension in which twitching contributes to sleep-dependent sensorimotor plasticity (Sokoloff et al., 2021).

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 early life has been documented in numerous vertebrate and invertebrate species. 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 co-opt numerous functions within its domain. Therefore, it is conceivable that the very first adaptive benefit that sleep conferred on an organism is buried far too deep in our evolutionary past—or too intermingled in the machinery of the cell—to ever be fully 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 resolve the many mysteries of sleep that are now within reach.

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