

What Is REM Sleep?

Mark S. Blumberg^{1,*}, John A. Lesku^{2,7}, Paul-Antoine Libourel^{3,7}, Markus H. Schmidt^{4,5,7}, and Niels C. Rattenborg^{6,*}

¹Department of Psychological and Brain Sciences, Iowa Neuroscience Institute, University of Iowa, Iowa City, IA 52242, USA

²School of Life Sciences, La Trobe University, Melbourne 3086, Australia

³Neurosciences Research Center of Lyon, CNRS UMR5292, INSERM U1028, University Claude Bernard Lyon 1 Neurocampus, 95 Boulevard Pinel, 69675 BRON, France

⁴Department of Neurology, Bern University Hospital (Inselspital), University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland

⁵Ohio Sleep Medicine Institute, 4975 Bradenton Avenue, Dublin, OH 43017, USA

⁶Avian Sleep Group, Max Planck Institute for Ornithology, Haus 5, Seewiesen 82319, Germany

⁷Contributed equally

*Correspondence: mark-blumberg@uiowa.edu (M.S.B.), rattenborg@orn.mpg.de (N.C.R.)

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For many decades, sleep researchers have sought to determine which species ‘have’ rapid eye movement (REM) sleep. In doing so, they relied predominantly on a template derived from the expression of REM sleep in the adults of a small number of mammalian species. Here, we argue for a different approach that focuses less on a binary decision about haves and have nots, and more on the diverse expression of REM sleep components over development and across species. By focusing on the components of REM sleep and discouraging continued reliance on a restricted template, we aim to promote a richer and more biologically grounded developmental–comparative approach that spans behavioral, physiological, neural, and ecological domains.

Introduction

Rapid eye movement (REM) sleep is many things. It is a behavioral state, a brain state, a dream state, and a paradoxical state. It is produced by complex and anatomically distributed neural circuits that give rise to a variety of individual components: muscle paralysis, rapid eye movements, an activated cerebral cortex, and so on. Do all these components — like the fork, spoon, and knife of a dinner setting — complement each other to achieve the same function? Or are they more like the varied tools in a Swiss army knife, gathered in the same place, but serving a variety of unrelated functions? If the latter, is there an underlying biological context of REM sleep (e.g., patterns of energy expenditure or gene expression) that explains why all its components are gathered within that one sleep state? Regardless, how do we explain that the individual components of REM sleep come and go across development and evolution, challenging efforts to determine its essential elements. Indeed, is REM sleep, in any meaningful sense, *a thing*?

It may seem odd that such basic questions about REM sleep are still being asked more than 65 years after its scientific discovery. But we — five sleep researchers with over a century of cumulative experience investigating sleep from diverse perspectives in diverse species (mammals, birds, and reptiles) across the lifespan, and in the wild, laboratory, and clinic — believe that these foundational questions remain stubbornly unresolved. Although the field has made tremendous strides in understanding REM sleep, it has done so by focusing primarily on adult humans, cats, and rats (and, more recently, mice). In the process, the field converged on a set of agreed-upon conventions that have made it possible to delve into the neurobiology of sleep and gain leverage in unmasking some of its functions. However, focusing on adults in a limited number of species can lull us into thinking that sleep in general — and REM sleep in particular — is easily defined and homogeneously expressed. In reality, REM sleep defies easy categorization. Physicians face this reality in

the sleep clinic, where pathological phenomena such as sleep-walking and ‘acting out dreams’ illustrate how the boundaries between sleep and wake states can be blurred and crossed [1]. But human pathology is not where REM sleep presents its greatest challenges. Rather, it is when we look to the diversity of sleep across species, ages, and environmental contexts that the inadequacies of current research conventions most clearly present themselves.

The first scientific report of REM sleep in 1953 was a seminal moment for the field [2]. When electrographic recordings revealed a surprising eruption of neural activity and rapid eye movements in the context of an otherwise sleeping, adult human, a new field was born. Long considered a passive state defined as the absence of wakefulness, the stage was set for reconsidering sleep as an active state (i.e., one in which energy is expended). This seemingly subtle shift in perspective laid the groundwork for many decades of discovery and, perhaps unavoidably, confusion. That confusion is easily illustrated by listing the many names assigned to this supposedly singular state of REM sleep — active sleep (in reference to muscular twitches and brain activation), desynchronized sleep (in contrast to the synchronized brain waves of non-REM sleep), paradoxical sleep (in reference to the paradox of wake-like cortical activity in a sleeping individual), rhombencephalic sleep (a nod to brainstem circuits driving the state), and dream sleep (even though dreaming also occurs in non-REM sleep). These labels reflect historical happenstance and the biases of the researchers who introduced them. In effect, each label represents a different attempt to capture the essential feature or features of this nebulous state. And now, today, the field is stuck with terminological confusion. For our purposes, the confusion of labels serves to illustrate our deeper concerns about the current state of the field.

For many decades, sleep researchers have catalogued and analyzed the behavioral and electrophysiological characteristics of sleep in diverse mammalian, avian, and reptilian species [3–6].

More recently, sleep in fishes, flies, and other ‘simple’ or ‘non-traditional’ organisms has become a topic of great interest [3–9]. One fact that emerged from these efforts is that REM sleep is a universal feature of terrestrial mammals, and that many of the features that define mammalian REM sleep are also found in birds [10]. Further support for the shared expression of REM sleep in mammals and birds comes from the dual observations that species in both vertebrate classes exhibit highly developed capacities to maintain a constant body temperature through the metabolic production of heat (i.e., endothermy) and also share the common feature of suspending temperature regulation during REM sleep [11,12]. Because of the evolutionary significance of endothermy and its high energetic costs, some researchers have hypothesized that the function of REM sleep is tightly coupled with the energetics of endothermy [13–17].

Against this backdrop came the recent startling claim that the Australian bearded dragon (*Pogona vitticeps*), a reptile, also has REM sleep [18]. Like all reptiles, the bearded dragon is an ectotherm and thus incapable of producing heat internally or suspending that capacity during sleep. Such a claim thus presents a stark challenge: We can refuse to accept that this lizard has REM sleep because it does not exhibit one of the core features of REM sleep (i.e., suspension of endothermy), or we can accept the claim and rely on it to falsify the hypothesis that REM sleep is intimately tied with the evolution of endothermy and its associated energetics.

The situation with the bearded dragon nicely encapsulates the challenge inherent in attributing REM sleep to taxonomic groups that lack certain key features of the state. It also unmasks a problem that has been lurking in the field for some time: we have spent too much time worrying about which species ‘have’ REM sleep without first arriving at a consensus as to what it actually means to make that claim.

Here, we argue that without a more comprehensive appreciation for the diversity and complexity of REM sleep, the functional and evolutionary significance of this fascinating sleep state will continue to elude us. Rather than focusing on the binary decision as to whether a species has REM sleep or not, we focus instead on the need to characterize the full diversity of its components, not merely the components resulting from a small sampling of mammalian species. By reframing the problem in this way, we aim to inspire a better understanding of how the individual components of REM sleep emerge and coalesce across development, how they relate to species-typical ecology and life-history patterns, and how they enhance survival and reproduction.

REM Sleep Today: Measures, Mechanisms and Functions

To say that REM sleep is a behavioral state is to say that it can be identified on the basis of observable features that coalesce in time. Consider an adult cat, curled up in a ball, largely unresponsive to the outside world. As it enters REM sleep, its head and limbs become completely slack (sleep paralysis), its eyes dart around beneath closed eyelids (rapid eye movements), breathing becomes irregular, and the limbs and whiskers twitch vigorously. Although we can observe these events with our own eyes, a researcher can measure these and other events electrophysiologically. Specifically, an electromyogram (EMG) implanted in

a neck muscle detects the loss of muscle tone (atonia), an electrooculogram (EOG) measures eye movements, and thoracic strain gauges or video recordings monitor respiratory irregularities; also, twitches can be detected with EMGs implanted in muscles, limb accelerometers, or video detection methods. But there is more to REM sleep than meets the eye. The electroencephalogram (EEG) reveals a highly activated cerebral cortex (similar to wakefulness), both during periods of twitching (‘phasic REM sleep’) and periods between twitching (‘tonic REM sleep’). Measures of peripheral metabolic activity reveal the suspension of internal heat production. And electrodes implanted deep in the brain reveal a host of additional features of REM sleep, including a prominent theta rhythm (4–8 Hz) in the hippocampus and activity within a brainstem neural circuit that produces sleep paralysis during this state (for review, see [19]).

In the 1960s, based largely on work in adult humans and several other mammals, a consensus emerged for defining REM sleep [20]. That consensus rested on three methodological pillars: EMG showing muscle atonia, EOG revealing rapid eye movements, and EEG demonstrating an activated cortex. Under routine circumstances, these three measures are sufficient to distinguish REM sleep from wake (high muscle tone, goal-directed eye movements, activated cortex) and non-REM sleep (moderate muscle tone, absence of eye movements, EEG slow waves). For most purposes, this consensus has held over the decades as it effectively distinguishes among the three primary behavioral states — at least in those animals that receive the lion’s share of attention.

Another emerging consensus concerns the specific neurobiological mechanisms that govern the expression of REM sleep (for review, see [19,21]). Briefly, neural circuits in the medulla, midbrain, and hypothalamus interact to initiate and terminate bouts of REM sleep and to control the expression of its various components. Across decades of investigation and the development of new methods for studying behaving animals, the fine details of REM sleep circuits have been revealed. Moreover, emerging from this network of interacting structures are descending and ascending projections to other parts of the nervous system that influence the expression of the various components of REM sleep, including muscle atonia, rapid eye movements, myoclonic twitches, and cortical activation. The influence of this circuitry can be striking: when humans or narcoleptic dogs experience a cataplectic event, the skeletal muscles of the body are suddenly inhibited, leaving them temporarily paralyzed, but fully aware of their surroundings [22]. Building on research with mice that were engineered to exhibit cataplexy [23], this phenomenon is presumed to involve the inappropriate activation of the sleep-paralysis component of REM sleep, which normally occurs in coordination with other REM sleep components. The fact that it is now possible to dissect the individual neural components of REM sleep to understand human pathology is one of the most impressive and exciting dimensions of modern sleep research [24].

Depriving mammals and birds of sleep leads to an increase in the pressure to sleep and subsequent rebound when sleep is allowed [25–27]. Such homeostatic regulation is often cited as evidence that sleep must serve important functions. The pressure to enter REM sleep is illustrated dramatically in horses, which are able to stand while in non-REM sleep, but must lie

down to safely enter REM sleep. However, when horses are reluctant to lie down, the pressure to enter REM sleep can be so strong that they do so while standing, resulting in a sudden loss of muscle tone and injurious falls [28].

Such examples of intense REM sleep pressure may speak to its functional importance. But, identifying those functions has proven elusive. Over the years, many theories have been posited, but few eliminated. Some theories attempt to explain REM sleep in its entirety [17,29]; others focus on just one (or a few) of its components [15,30,31]. Still others, noting how adult mammals typically cycle back and forth between REM and non-REM sleep within a single sleep period, posit that the two sleep substates perform complementary or compensatory functions [32–34]. Nevertheless, today there is little agreement as to what form a functional theory should take.

After REM sleep was first characterized in adult humans, it did not take long to recognize that it is most prevalent in early human development — being the dominant brain state in fetuses. At birth, the daily allotment of REM sleep in humans is eight hours — similar to wake and non-REM sleep — and declines to approximately two hours in adults [31]. The relative predominance of REM sleep in early development inspired the *ontogenetic hypothesis*, which posits that REM sleep serves a uniquely important function for the developing brain [31]. In time, it became clear that REM sleep is highest in the infants of altricial mammals, such as rats and cats, that are born relatively immature [35]. Similarly, a relative abundance of REM sleep is observed in young altricial birds [36]. In our opinion, this seemingly universal feature of REM sleep must be considered by any theory that aspires to provide a comprehensive explanation of its function.

The ontogenetic hypothesis has inspired numerous experiments aimed at understanding how REM sleep contributes to developmental plasticity. For example, REM sleep is implicated as a causal factor in regulating plasticity in the visual cortex of rats and cats [37,38]. Also, REM sleep — especially the abundant limb twitching that characterizes this state in early infancy — may be particularly important for the self-organization of the sensorimotor system and the establishment of functional connections across distant structures in the brain [39–41]. In addition, it is likely that the functional contributions of REM sleep to neural plasticity are not confined to early development; instead, there may be continuity across the lifespan with regard to the cellular and molecular plasticity mechanisms recruited during REM sleep.

Attempts to understand the functions of REM sleep, and its components, led to the long-standing interpretation that the sleep paralysis characterizing this state protects against ‘acting out dreams’ [30] (see also [42]); it is difficult, however, to maintain this popular theory given the now-accepted view that dreams are not restricted to REM sleep [43].

Arguments for memory processing during REM sleep continue to gain traction: For example, the prominent theta rhythm in the mammalian hippocampus during REM sleep is thought to promote such consolidation [44]. REM sleep may also play a role in modulating the pruning and maintenance of new synapses during the process of learning new motor skills [45]. Finally, REM sleep appears to play a role in regulating emotions during subsequent wakefulness in humans [46,47].

At a much broader level than most other approaches, the *energy allocation hypothesis* posits that REM sleep should be considered within the larger context of each animal’s energetic needs for growth, maintenance and repair, neural plasticity, and reproduction [17]. These needs fluctuate across the day, and each behavioral state — including REM sleep — is uniquely suited to meet the animal’s particular biological requirements at the moment. These functions range from the need for vigilance while awake to macromolecule biosynthesis [48], chromosome repair [49,50], and memory consolidation during sleep [44,51]. The selective upregulation and downregulation of gene expression across sleep–wake states also falls within the purview of this perspective [52].

According to the *energy allocation hypothesis*, sleep and wake states are behavioral strategies that promote efficient, whole-organism, resource allocation. The types of functions coupled with each state are predicted to vary across species in relation to specific selection pressures. The optimization of resource allocations may occur not only across sleep and wake, but also within sleep through non-REM–REM sleep cycling. Specifically, mammals and birds may dynamically modulate REM sleep expression such that it optimally occurs when the need for costly thermoregulatory defense is minimized [53]. The resulting efficiencies in resource utilization allow organisms to do more at less energetic cost [54,55]. Accordingly, each animal regulates its efficient use of energy across the day and across its lifespan in the service of optimizing survival and reproductive success.

Developmental Challenges to Understanding REM Sleep

To achieve a satisfying understanding of REM sleep, the challenges presented by its development and its species-typical expression must be considered. Ideally, given that evolution occurs through modifications of developmental processes [56–58], we advocate a developmental–comparative approach. One sleep pioneer, Michael Corner, was an early proponent of such an approach. Corner observed and compared the behavior of numerous vertebrate and invertebrate embryos. He noted that behavior invariably begins as rapid cycles of spontaneous motility, several per minute, developing and morphing over time into more organized bursts of activity [59,60]. He concluded that phasic post-embryonic events of REM sleep — such as rapid eye movements and limb twitches of mammals and birds — are best characterized as the postnatal expression of an ancient and fundamental feature of behavioral development across the animal kingdom.

Nonetheless, as a behavioral state, REM sleep is more than simply a series of movement cycles. As discussed, this state comprises muscle atonia, an activated cortex, a hippocampal theta rhythm, suppression of thermoregulatory mechanisms, and so on. But these varied components of REM sleep are not all present at the beginning. On the contrary, they arise through a developmental process — emerging and coalescing over time — to form the adult state of REM sleep. A comprehensive theory of REM sleep should address why some of its components, but not others, predominate in early life; why certain components emerge at particular stages of development and why they are (or are not) expressed in different species; and why certain

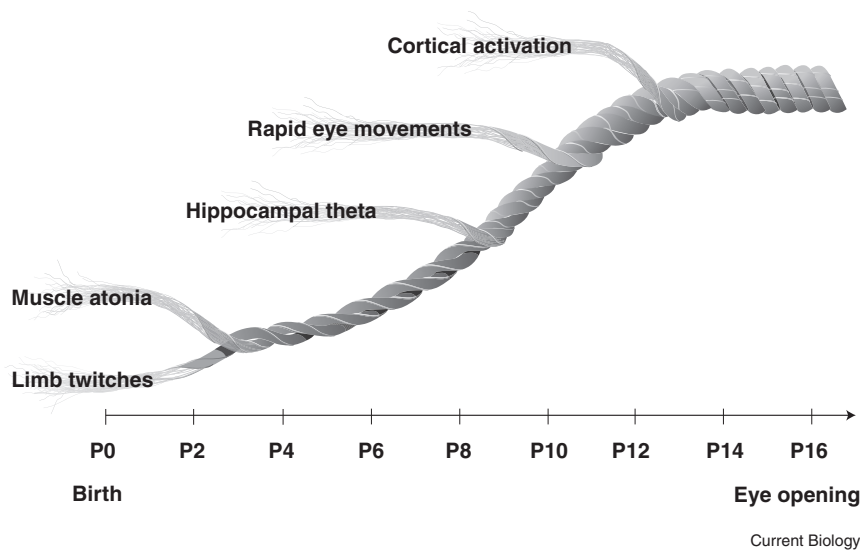


Figure 1. Coalescence of REM sleep components over development in infant rats.

In early postnatal development in rats, the various components of REM (active) sleep emerge in succession, coalescing with others over time to increase the resemblance to the more familiar state of REM sleep in adults. Figure adapted and updated from [67]. See text for details. P, postnatal day.

components have evolved to couple with REM sleep instead of non-REM sleep or wake.

The developmental coalescence of REM sleep components has been described most comprehensively in infant rats [61]. At birth, pups exhibit cycles of myoclonic twitching, similar to the embryonic motility described above. Unlike the high-amplitude coordinated movements of awake pups when muscle tone is high, twitches occur against a background of muscle atonia by postnatal day (P) 2 [62]. The coordination between twitching and muscle atonia is the first clear indicator of the REM sleep state in early infancy. The whiskers of infant rats also twitch, exhibiting patterns of movement similar to those exhibited by the limbs [63].

Although the eyes of newborn rats are immobile behind sealed eyelids until P15, measures of extraocular muscle activity reveal signs of twitching similar to that observed in the limbs [64]. Importantly, extraocular and limb muscle twitches occur in contemporaneous bursts. Then, as the eyes gain mobility before eye opening, spikes detected in the extraocular muscles trigger eye movements. The continuity between extraocular muscle twitches and the subsequent emergence of rapid eye movements provides evidence of developmental continuity underlying the REM sleep state.

Muscle atonia and twitching provide compelling evidence of REM sleep at ages when other components are conspicuously absent. Most notably, cortical EEG at these early ages exhibits a discontinuous pattern, defined as long periods of neuronal silence interspersed with brief bursts of activity. At these ages, the cortical EEG exhibits none of the synchronized and desynchronized features that, at later ages, help to define sleep and wake states. However, when the EEG finally exhibits REM sleep-like features around P11, they immediately cohere in time with twitching and muscle atonia [65]. As another example, the hippocampal theta rhythm does not develop until after P8, beginning as brief bursts of theta that follow twitches [41,66]. Shortly after P8, these brief theta bursts transform into continuous waves of theta that span entire periods of twitching. Moreover, the theta observed in the hippocampus is tightly coupled with a similarly developing theta rhythm in the red nucleus, a

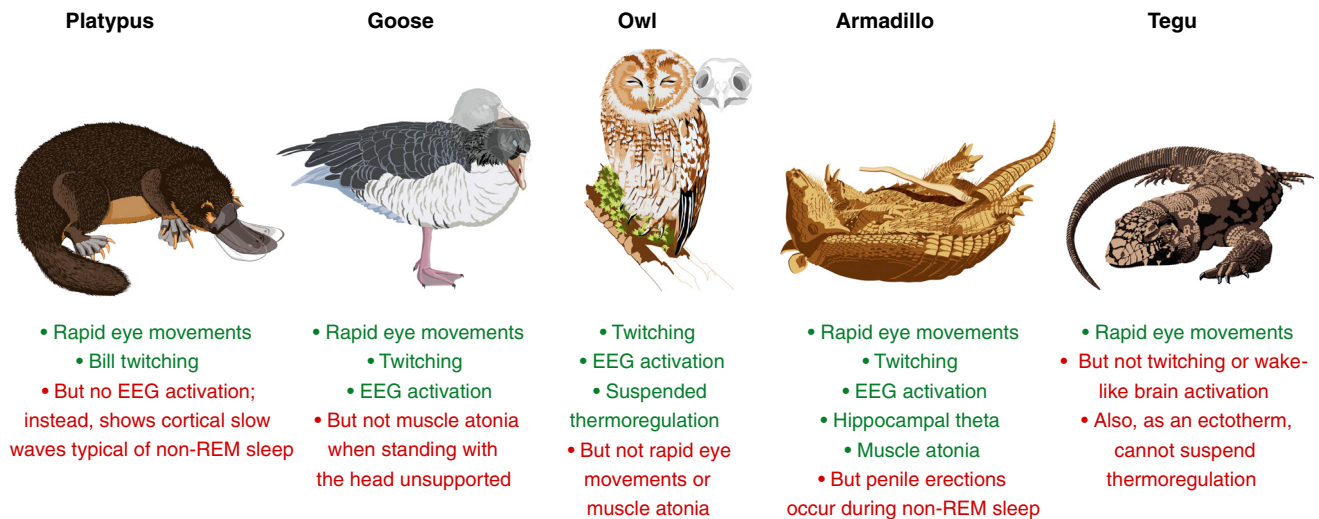
brainstem motor nucleus that itself contributes to the production of twitching. Invoking a metaphor first introduced by Corner [67], these examples illustrate that REM sleep is like a rope comprising multiple strands, each strand emerging in development and cohering with those already in place (Figure 1).

Although sleep homeostasis — especially as measured by a rebound in

cortical slow-wave power during non-REM sleep — and circadian regulation are together considered key regulatory features of sleep in adult mammals and birds [27,68], they also exhibit complex developmental profiles. For example, as early as P2 in rats, nine days before the cortical slow waves of non-REM sleep are first detected, both key features of sleep homeostasis — pressure and rebound — are present. Also, at this age, sleep and wake bouts are highly fragmented, resulting in rapid ultradian cycles that can be as brief as 20 seconds. Then, over the next two weeks, sleep and wake bouts gradually consolidate and, by P15, circadian regulation of sleep–wake cyclicity is evident (for review, see [69]).

Thus, considering both the components of REM sleep and the processes that regulate it, the developmental reality of REM sleep impedes our efforts at arriving at an ironclad definition of this state. On the one hand, if we hold too tightly to a set of ‘essential’ criteria to define the state, we are forced to argue that neonatal REM sleep is not ‘real REM sleep’ until all the essential criteria are met (e.g., at P11 in rats with the emergence of a desynchronized cortical EEG). On the other hand, as we look earlier and earlier in development, we confront fewer and fewer components until, in the embryo, perhaps only one remains. Whereas the former scenario relies on an arbitrary criterion for defining REM sleep, the latter forces us to confront the challenge of maintaining a biologically coherent definition of REM sleep as it changes quantitatively and qualitatively across development.

Regardless, one thing is clear: To achieve a comprehensive understanding of REM sleep, we must learn more about sleep ontogeny across many species spanning diverse taxonomic groups. After all, we should not expect the developmental details of REM sleep in rats to generalize across rodents and other mammals, let alone across birds and other vertebrates. But also, as we turn now to the complexities of REM sleep expression across species, we encounter an even broader array of challenges to the notion that there exists a consistent set of criteria that accurately captures the state of REM sleep.



Current Biology

Figure 2. Animals that challenge traditional definitions of REM sleep.

The platypus exhibits a single mixed sleep state consisting of bill twitching and rapid eye movements (typical of REM sleep) even as the cortical EEG exhibits slow waves (typical of non-REM sleep). Rather than exhibiting atonia across all skeletal muscle groups — traditionally a defining feature of REM sleep — geese and other birds often sleep with their head unsupported and show only partial reductions in neck muscle tone, which causes the head to drop during REM sleep, but they sustain the muscle tone required to balance on one foot. Owls engage in REM sleep typical of most birds but lack rapid eye movements because their eyes are largely immobile within the skull (inset). Armadillos exhibit two sleep states that readily conform to traditional definitions of non-REM and REM sleep, except that penile erections (which are tightly coupled with REM sleep in humans and rats) occur during non-REM sleep. In contrast to the wake-like brain activity that traditionally defines REM sleep, sleeping tegus exhibit a novel 15-Hz brain oscillation, associated with rapid eye movements, that is not present during wakefulness. Also, as an ectotherm, they cannot suspend thermoregulatory effectors (e.g., sweating, shivering) like endothermic mammals and birds do during REM sleep.

Comparative Challenges to Understanding REM Sleep

The challenges of defining REM sleep do not end when animals reach adulthood. An examination of sleep in adults across a variety of species reveals largely underappreciated diversity in how sleep is expressed. In particular, components traditionally used to define REM sleep may only be partially expressed in some species or altogether absent (Figure 2). In some cases, REM sleep components may sporadically intermingle with the large, slow EEG waves that define non-REM sleep, or even become unmoored from REM sleep altogether and associate instead with non-REM sleep. And then there are cases where potential REM sleep components are wholly unique to a species and completely absent in close relatives.

Species with Partial Expression of REM Sleep Components

It is widely acknowledged that birds exhibit two sleep states similar to the non-REM and REM sleep states observed in mammals [10,70–74]. In birds, non-REM sleep consists of homeostatically regulated EEG slow waves that become larger after long periods of wake and become smaller with sleep [27]. As in mammals, slow waves also become more prominent in brain regions that receive greater stimulation during prior wakefulness [75]. Furthermore, avian slow waves travel across the brain, similar to the travelling slow waves in mammalian cortex [76]. Also, transitions from non-REM to REM sleep in birds are characterized by the onset of eye movements under closed eyelids, twitching, wake-like brain activity, wobbling and head drops that reflect reduced muscle tone, variable cardiac and respiratory rhythms, and suspension of thermoregulatory responses [11,12,36,72,73]. Despite these similarities,

REM sleep episodes are very short in birds, typically lasting less than 10 seconds.

Birds also differ from mammals in that one of the key components of REM sleep — muscle atonia — is only partially expressed [73] (reviewed in [77]). Birds typically exhibit a variety of sleep positions that require some degree of active postural control and are, therefore, incompatible with muscle atonia. Unlike large mammals, such as horses, giraffes, and elephants, that can stand during non-REM sleep but must lie down during REM sleep [28], birds can stand in either sleep state, even while balancing on one foot. In addition, sleeping birds may orient their head in a forward position (unsupported), or rest it on the shoulder (partially supported) or back (fully supported). Ostriches (*Struthio camelus*) are exceptional in that, during REM sleep, they can hold their heads high above the ground, periscopically extended on long necks [78].

To explain the unique ability of birds to sleep while standing on a perch, researchers once proposed that birds possess a special locking mechanism in the legs to passively maintain their grip. The locking mechanism, however, was called into question by experiments showing that anesthetized or freshly euthanized starlings (*Sturnus vulgaris*) do not passively hold onto a perch [79]. Instead, during REM sleep, the birds maintain muscle tone to keep balance and stay upright; in some instances, they even withdraw one leg toward the body. In contrast to the muscles that control legs, neck muscles that support the head can show modest reductions in tone during REM sleep (hypotonia). In various species, including great frigatebirds (*Fregata minor*) during soaring flight [80], the head drops to varying degrees when in REM sleep with the head facing forward, reflecting

partial relaxation of the neck muscles. Similar head drops and neck muscle hypotonia also occur in sleeping ostriches and geese (*Anser anser*) when the head is unsupported [73,78]. But when geese rest their head on their back, the neck muscles exhibit mammal-like atonia. Thus, although the neural mechanisms involved are still unknown, birds differentially regulate the extent to which muscle atonia is expressed, and they do so in a posture-dependent manner.

Species with Complete Absence of REM Sleep Components

Other animals have completely lost components of classically defined REM sleep, or never had them in the first place. Although birds, like mammals, exhibit cortical activation during REM sleep [76], there is no evidence that they exhibit a hippocampal theta rhythm. The lack of theta may be due to differences in the neuronal organization and function of the hippocampus in birds and mammals [81]. The absence of certain REM sleep components may also be due to evolutionary specialization or regression of the systems involved in a particular REM sleep component. For example owls — like other birds — exhibit REM sleep characterized by EEG activation, twitching, reduced muscle tone (head drops), and suspended thermoregulation [36,82]. However, owls lack rapid eye movements during REM sleep because their extremely large tubular eyes, encircled by a large ring of rigid bone, are almost completely fixed within their eye sockets [83]; the unique size and shape of their eyes makes owls better able to hunt at night [84]. Rapid eye movements are also precluded, though for different reasons, in blind mole rats (*Spalax ehrenbergi*) [85] and moles (*Scalopus aquaticus* and *Condylura cristata*) [86]: as fossorial mammals, moles and mole rats have evolved to live almost entirely underground and their visual systems have regressed.

REM Sleep Components Intermingling with Non-REM Sleep Components

In addition to the loss of a REM sleep component or its partial expression in some species, other REM sleep phenomena may intermingle with non-REM sleep components. The cortical EEG provides the clearest evidence of intermingling, perhaps because its slow-wave pattern of activity during non-REM sleep is so distinct. For example, the sleeping platypus (*Ornithorhynchus anatinus*) exhibits rapid eye movements and twitches of the head and bill [87]. However, during these periods, the cortical EEG exhibits slow waves typical of non-REM sleep in other mammals. The absence of cortical activation during REM sleep presents a quandary: does the platypus express a lot of REM sleep as assessed by the high rate of twitching, or does it express very little REM sleep as assessed by the absence of an activated EEG?

Ostriches also exhibit the platypus-like mixed state; however, unlike the platypus, sleeping ostriches also show the more typical REM sleep pattern of EEG activation accompanied by rapid eye movements and reduced muscle tone [78]. However, the periods with the most pronounced EEG activation do not include the most substantial reductions in EMG activity. As with platypuses, ostriches push conventional definitions of REM sleep to their limits.

In addition to the mixed sleep states found in ‘exotic’ animals like the platypus and ostrich, even laboratory rodents reveal an unexpected blurring of the lines between REM and non-REM

sleep. Specifically, whereas EEG recordings from the surface of the brain during REM sleep suggest that the entire cortex is activated uniformly, more sensitive recordings — using electrodes implanted within the cortex — reveal the presence of slow waves as well. The slow waves are localized to those layers in sensory cortex that receive direct input from the thalamus [88]. Such localization may be specific to mice, rodents, or perhaps mammals in general, as the thalamic input layers of the pigeon hyperpallium — the avian homologue of the mammalian primary visual cortex — do not exhibit localized slow waves during REM sleep [76]. Variation in the timing of REM sleep among brain regions can also cause components of REM and non-REM sleep to intermingle. In sleeping rats, the hippocampus and cortex frequently appear to be in different sleep states, with the hippocampus often transitioning to REM sleep before the cortex [89,90]. Thus, although intermingling of sleep components is more conspicuous in the platypus and ostrich, it may be more widespread than typically recognized.

In some species, components can completely lose their association with REM sleep and become exclusively linked with non-REM sleep. For example, penile erections occur during REM sleep in humans and rats [91–94]. However, the association between erections and REM sleep does not hold across mammals. Armadillos (*Chaetophractus villosus*) exhibit most of the classical components of REM sleep, including EEG activation, hippocampal theta, muscle atonia, irregular respiration, rapid eye movements, and twitches of the limbs and whiskers [95]. Although male armadillos also have erections during sleep, they occur during non-REM sleep. In rats and humans, the skeletal muscles involved in erections (see [96]) become active during REM sleep [93,97], whereas in armadillos the erectile muscles become atonic [95], as with other skeletal muscles. We do not yet fully understand the mechanisms that give rise to armadillo erections during non-REM, rather than REM, sleep. Also, the functional implications of this difference in penile muscle control are unclear. But the armadillo does illustrate how the unique physiology of a species can substantially alter the expression of a REM sleep component, even when that component is tightly and consistently associated with REM sleep in other species.

The Curious Case of REM Sleep in Marine Mammals

Thus far, we described species that appear to exhibit a form of REM sleep in which one or more ‘standard’ components are lacking. But we have not yet considered the cetaceans — marine mammals such as dolphins and whales — for which clear evidence of REM sleep is lacking. There is some behavioral evidence for REM sleep in adult whales and dolphins, which exhibit eyelid movements, twitches, and erections during sleep [98]. There is also one report of an episode of REM sleep, characterized by EEG activation and loss of trunk muscle tone, in a pilot whale (*Globicephala scammoni*) [99]. No other EEG-based recordings in cetaceans have revealed unequivocal signs of REM sleep [98]. Possibly, the unnatural recording conditions in these studies were incompatible with the expression of REM sleep, as occurs in other mammals and birds [100,101]. It is also possible that life in the water is not conducive to the full expression of REM sleep in some species [102]; this possibility is most clearly supported by evidence that captive fur seals (*Callorhinus ursinus*) exhibit REM sleep while on

land, but very little when forced to sleep in seawater for two weeks [103].

If REM sleep, accompanied by suspended thermoregulation, is critical for brain development, the high thermal conductivity of water seemingly poses a conundrum for newborn cetaceans [102,104]. Bottlenose dolphins (*Tursiops truncatus*) and killer whales (*Orcinus orca*) are highly precocial: immediately after birth they can see, swim, and surface to breathe. In fact, they swim virtually continuously during the first postnatal month, thus raising the question of whether they sleep at all during this time in early development [105]. In fact, newborn dolphins close one eye while swimming underwater, suggesting that they engage in non-REM sleep with one half of the brain at a time [106,107], as is known to occur in all adult cetaceans studied thus far [103]. However, assuming that loss of muscle tone is a reliable component of REM sleep in mammals, it seems as though newborn dolphins do not exhibit REM sleep [105]. If true, continuous swimming in newborns could call into question the importance of REM sleep for early brain development. However, caution is warranted: as with precocial terrestrial mammals, we expect that the amount of REM sleep in precocial marine mammals would be low at birth and, indeed, throughout life [108]. Moreover, infrequent REM sleep after birth does not preclude the expression of large amounts of REM sleep *in utero*, as is known to be the case in other precocial mammals, such as guinea pigs [109]. Consequently, as an adaptation to living and sleeping at sea, the role of REM sleep in brain development might be limited primarily to the prenatal period in cetaceans. Regardless, cetaceans powerfully illustrate how ecological factors and life-history patterns must be considered when assessing the presence or absence of REM sleep, and its components, in a given species.

Reaching Further Back in Evolutionary Time for the Origins of REM Sleep

There is broad consensus today that both mammals and birds exhibit REM sleep. If this consensus is correct, we would next want to know how the similar sleep patterns in such distantly related groups evolved. Mammals and birds have not shared a common ancestor for over 300 million years. Did REM sleep evolve independently in the mammalian and avian lineages, or was REM sleep present in a common ancestor? Researchers have long tried to answer this question by recording sleep behavior and brain activity in non-avian reptiles, amphibians, and fishes. Unfortunately, this work has often yielded contradictory results [110–112].

Two recent studies in lizards suggest that contradictions in the earlier literature reflect genuine diversity in the way sleep manifests across reptiles. Shein-Idelson and colleagues [18] recently reported the existence of REM sleep in the Australian bearded dragon. Brain activity in this sleeping lizard alternates with astonishing regularity — every 80 seconds — between equal-length periods composed of sharp waves and wake-like brain activity with isolated eye movements (called ‘eye twitches’) under closed eyelids. Limb twitches were not reported. Shortly after this initial description of REM-like sleep in the dragon, these findings were replicated in the same species by another research group [113]. This second team also found that another lizard, the tegu (*Salvator merianae*), exhibits a REM-like sleep state, including distinct brain activity associated with eye movements (rare limb twitches

were observed but were not unambiguously related to the state). However, the two species showed marked differences in the REM-like sleep state. Whereas brain activity in the dragon was characterized by high power across a broad range of frequencies (10–30 Hz), similar to that observed during wakefulness, brain activity in the tegu exhibited a distinct 15-Hz peak not found during wake. Moreover, in contrast to the precisely regular alternation between sleep states in dragons, tegus showed no such regularity.

Although the reasons for the stark differences in the two lizards are unknown, the studies further underscore the challenge of finding consensus on the defining features of REM sleep: if these two lizard species exhibit such diversity, what should we expect as more reptiles are studied? Will their sleep patterns converge on a shared set of characteristics that resemble REM sleep in mammals and birds? And how should we interpret previous studies that failed to detect a REM-like state in crocodilians, the closest living relatives to birds, and in turtles, the sister group to birds and crocodilians [110,111]? Although it is possible that the earlier studies in crocodilians and turtles were somehow flawed, we should not simply ignore these exceptions. In the end, when attempting to trace the evolution of REM sleep, we must account for the full taxonomic diversity of sleep and its seemingly patchy phylogenetic distribution.

But now, again, yet another recent paper claims to have pushed the evolutionary origins of REM and non-REM sleep even further back in time — to 450 million years ago. Using larval zebrafish (*Danio rerio*), Leung and colleagues [9] developed an impressive whole-body fluorescence method to measure neural activity throughout the brain of these transparent animals while restrained in agar. In addition to brain activity, they measured muscle activity, eye movements, and heart rate. Two sleep states were reported: the first state, most clearly defined after sleep deprivation, is characterized by synchronous bursts of activity alternating with periods of silence in the dorsal pallium (a homologue of neocortex), reminiscent of the bursts of activity during mammalian and avian non-REM sleep (albeit on a much slower timescale). The onset of the second spontaneous state is characterized by a single contraction of the trunk muscles lasting 10–15 seconds and a single, prolonged (up to 5 min) burst of activity that propagates through the central nervous system. The authors call this state propagating wave sleep (PWS). It should be noted that the long-lasting muscle contractions that occur at the onset of brain activation are unlike the brief twitches that characterize mammalian REM sleep. Also, brain activity after a burst in the zebrafish was suppressed below waking levels for more than 20 minutes. Another peculiarity is that rapid eye movements did not occur during spontaneous PWS, even though the eyes moved freely during wakefulness. Thus, although these bursts of activation are fascinating, it is unclear if and how they relate to REM sleep in mammals and birds.

Additional hints suggest that components of REM sleep emerged even farther back in evolutionary time. For example, a variety of insects — from larval flies to adult bees — twitch their antennae during states that resemble sleep [114–117]. But such observations alone do not constitute clear evidence of homology between invertebrate and vertebrate sleep states. After all, not all movements during sleep are twitches; nor do we have sufficient

information about the nervous systems of sleeping insects to understand what these twitch-like movements represent.

Twitching is also apparent in resting cuttlefish (*Sepia officinalis*), but in a way that is remarkable and unique. When awake and swimming, cuttlefish exhibit choreographed patterns of coloration for communication and camouflage [118]. The changes in color and pattern are mediated by chromatophores — pigment-containing skin cells that are controlled by striated muscle. While apparently asleep, cuttlefish initially rest motionless on the seafloor with their pupils constricted and their coloration cryptically matching the surrounding substrate [119,120]. Such periods of quiet rest are occasionally interrupted by prolonged (2–3 minute) bouts of twitching of the tentacles, eyes, and — astoundingly — the chromatophores, resulting in rapid changes in coloration and patterning that announce, rather than conceal, their presence (similar patterns of chromatophore activation during apparent sleep have been reported in the octopus [121,122]). Although arousal thresholds have not been assessed to rule out the possibility that the cuttlefish behaviors reflect brief awakenings, the patterns of chromatophore activation bear little resemblance to what is observed when cuttlefish are clearly awake. If, in fact, they are asleep, further work on cuttlefish may provide novel insights into the evolution of REM-like sleep states, especially given the independent evolution of complex brains, behavior, and cognition in cephalopods [123]. When combined with research on relatively ‘simple’ mollusks [124], this research raises the hope of revealing the independent and convergent evolution of individual components that comprise REM sleep.

Conclusion: Reframing REM Sleep

We have highlighted here the many exceptions to the classical view of REM sleep to underscore the challenges that lie ahead as sleep is investigated in an increasingly wide array of species. On the one hand, we endorse any effort to reveal the neural and behavioral processes of sleep in non-mammalian and non-avian species. On the other hand, we are disappointed when these efforts encourage hasty proclamations regarding the evolutionary origins of REM sleep. Potentially informative differences are often downplayed and conflicting findings from earlier studies that might frustrate the telling of simple stories about the evolution of sleep are often ignored. Even when discoveries of purported REM sleep in a new species are accompanied by the requisite caveats, and contradictory findings are acknowledged, the take-home message is that the boundaries of REM sleep have been definitively expanded.

In part, the current situation is driven by a ‘model-species’ approach to comparative research in which the value of a newly investigated species for sleep research is deemed useful only to the extent that its sleep resembles that of mammals. One consequence of this perspective is pressure to emphasize similarities between the studied organism and adult mammals. Indeed, we have all felt (and occasionally succumbed to) the pressure to justify or ‘translate’ our work in this way. Further adding to the problem, sleep researchers and manuscript reviewers seem to pick and choose which mammalian sleep components they deem necessary or sufficient to conclude that a given species or phylogenetic group ‘has’ REM sleep. For example, the first published description of REM sleep in birds was rejected by

the journal *Science*, in part, because the reported REM sleep episodes did not adhere to the mammalian standard: the birds’ REM sleep episodes were too brief and they did not exhibit complete muscle atonia (Ookawa, personal communication); the paper was ultimately published in *Poultry Science* [71] (see also [70]).

The surest path through this thicket of diverse REM sleep components, and their diverse means of expression, is to resist the temptation to make forced-choice decisions as to whether a species ‘has’ REM sleep. For example, the fact that birds only show partial reductions in muscle tone should not be viewed as a disqualifying feature, but rather embraced as an opportunity to gain comparative insight into the mechanisms and functions of muscle tone regulation during sleep. Through such truly comparative assessments, we will be on a much firmer footing to discover general principles of sleep that apply to birds *and* mammals *and* other taxonomic groups — principles that are beyond our grasp if species with divergent sleep characteristics are forced to conform to researchers’ adult- and mammal-centric expectations. Indeed, as we consider a broader range of possibilities for describing and classifying sleep states across the animal kingdom, we may come to realize that some phylogenetically distant species exhibit completely unique vigilance states that do not conform in any meaningful way with REM or non-REM sleep as defined in mammals and birds.

The value of comparative research lies in diversity. Comparisons across species, young and old, with and without the full complement of conventional sleep characteristics, promises to provide new insights into the phenomenological and functional features of REM sleep and how they have evolved to serve specific requirements across diverse taxonomic groups. Just as curiosity about sleep in dolphins led to the discovery of unihemispheric non-REM sleep [125] and a paradigm shift toward viewing non-REM sleep as a locally regulated process [43,75,77,126–128], a pan-animal kingdom approach to understanding the diversity of REM sleep will accelerate progress toward answering the question of what REM sleep really is.

What is the way forward? We hope that our review will embolden researchers to move beyond mere labelling of REM sleep toward a greater focus on understanding the mechanisms, development, and evolutionary history of the components, including those that diverge from the mammalian template. We need to know more about which sleep components co-occur because they are functionally complementary, as with the fork, knife, and spoon in a dinner setting. We also need to know which sleep components co-occur but lack any obvious functional connections, as with the screwdriver, scissors, and corkscrew in a Swiss army knife. And even with no obvious functional connection between two sleep components, there may be a deeper rationale for their co-occurrence that involves common constraints related to such factors as energy efficiency or gene expression. By leveraging the diversity of REM sleep across the lifespan in diverse species, we can leave behind debates about ‘haves’ and ‘have-nots’ and accelerate toward a deeper understanding of mechanisms and functions that a truly developmental and comparative science of sleep will afford.

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