OPINION

Exploring phylogeny to find the function of sleep

Ron C. Anafi, Matthew S. Kayser and David M. Raizen

Abstract | During sleep, animals do not eat, reproduce or forage. Sleeping animals are vulnerable to predation. Yet, the persistence of sleep despite evolutionary pressures, and the deleterious effects of sleep deprivation, indicate that sleep serves a function or functions that cannot easily be bypassed. Recent research demonstrates sleep to be phylogenetically far more pervasive than previously appreciated; it is possible that the very first animals slept. Here, we give an overview of sleep across various species, with the aim of determining its original purpose. Sleep exists in animals without cephalized nervous systems and can be influenced by non-neuronal signals, including those associated with metabolic rhythms. Together, these observations support the notion that sleep serves metabolic functions in neural and non-neural tissues.

The death of each day's life, sore labour's bath,
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast.
Macbeth (2.2.50–52)

In three short lines, William Shakespeare captures the diverse spirit of contemporary theories regarding the function of sleep. The "death of each day's life" reflects the null hypothesis that sleep serves no particular function but is simply an absence of wake. The phrases "sore labour's bath" and "Balm of hurt minds" imply that sleep functions in the repair of body and brain, respectively. "nature's second course" suggests a more vital and specific role for sleep, one not served by wake. Shakespeare ends by suggesting that sleep is singularly essential to wake-time functioning, describing it as the "Chief nourisher in life's feast".

Humans were the focus of Shakespeare's literary observations, and most of the modern scientific debate on the purpose of sleep has similarly centred on human sleep. However, researchers have identified sleep in every animal carefully examined. Sleep has been described in the phyla Chordata[1], Arthropoda[2], Nematoda[3], Mollusca[4], Platyhelminths[5] and Cnidaria[6]. To understand sleep and its function, we must redirect our focus to span the tree of animal life.

Although much work regarding the function of sleep has relied on studies of the consequences of sleep deprivation, this approach has limitations (BOX 1). The study of sleep across phylogeny provides an alternative approach to understanding sleep function. The phylogenetic framework depends on the postulation that sleep states emerged early in animal evolution (FIG. 1a), such that mechanistic insights gleaned from evolutionarily distant species are informative regarding principles of sleep in all animals. Specifically, examination of sleep in different species may enable the distillation of the core functions of sleep.

The goal of this article is to provide an overview of sleep states identified in different species, highlighting the fact that certain functional aspects are probably conserved from an ancestral sleep state. This conservation, coupled with recent observations of the effects of sleep on non-neural tissues as well as the control of sleep by non-neural tissues, suggests that sleep evolved fundamentally as a metabolic state of the animal and serves functions outside the nervous system. We discuss these metabolic roles of sleep in the context of sleep phylogeny. As previously proposed, metabolic roles of sleep include a means for saving energy[7], temporally separating chemically incompatible reactions[8,9], allocating metabolic resources[10] and maximizing the efficiency of metabolic processes. Several clinical observations[11–13] also support the notion that sleep serves metabolic roles in humans.

Sleep across phylogeny

Electroencephalographic (EEG) signals in mammals and birds provide surrogate markers for sleep states, whereby wake is characterized by mixed-frequency low-voltage signals, and deep non-rapid eye movement (NREM) sleep is characterized by low-frequency high-voltage EEG oscillations. However, at its core, sleep is defined behaviourally: sleep is a quiescent behavioural state associated with reduced responsiveness to weak stimuli and rapid reversibility in response to strong stimuli[14]. The reduced sensory responsiveness during sleep distinguishes it from immobility during wakefulness, and the rapid reversibility of the quiescent state distinguishes sleep from other physiological and pathophysiologic quiescent states such as torpor, hibernation, tonic immobility and coma (TABLE 1). Following sleep curtailment, some animals sleep more deeply[3,15], whereas others extend the duration of their sleep or sleep at inappropriate times[16,17]. This behavioural response to sleep deprivation, which is mediated through so-called sleep homeostasis, is another central element of sleep, and its presence provides prima facie evidence of sleep's importance.

The invertebrate first suggested to display a behavioural sleep state was the cockroach *Leucophaea maderae*, which, when forced to continue locomotion during its resting time, showed an increase in subsequent immobility[2], suggesting homeostatic guarding of the resting behavioural state. A follow-up study showed that immobility during the inactive period was associated with a reduced level of arousal[18], as would be expected for a sleep state (TABLE 1). In the honeybee (*Apis mellifera*), a similar quiescent behavioural state with reduced arousability was associated with decreased responsiveness of visual interneurons, demonstrating a physiological basis to this behaviour[19].

The modern era of mechanistic studies of sleep began at the turn of this century

Box 1 | **What can we learn from sleep deprivation experiments?**

The homeostatic guarding of sleep, which is observed in sleep deprivation experiments, demonstrates that sleep serves an important function that cannot easily be bypassed. Thus, sleep deprivation experiments performed in humans[77], rats[138], mice[115,118], fruitflies[139] and roundworms[49] have been used in an attempt to infer the function of sleep, with the logic that when sleep is removed, so too will its underlying function[140]. Mammalian neural tissue and non-neural tissues (including pancreatic endocrine cells, fat tissue, immune cells and skin) are all affected by sleep deprivation[12,138,141–143]. Total sleep deprivation for several days in rats results in a hypermetabolic state (in which weight loss was observed despite increased food intake), skin breakdown, multi-organ failure and eventual death[144].

By the above reasoning, the results of sleep deprivation experiments can be interpreted to indicate that sleep is required for memory formation[145] and brain plasticity[146], for supporting neuron viability[147], for promoting insulin release and insulin responsiveness[148], for thermo-regulation[140] and for maintaining immune[149] and skin[140] function.

However, observing the consequences of sleep deprivation does not necessarily reveal the normal functions of sleep. The emotional stress, elevated muscular activity and changes in temperature and diet associated with sleep deprivation protocols probably have independent effects. Mechanical stimuli used to sleep-deprive fruitflies and roundworms may injure the animals[25,89,139]. More generally, physiological processes are often closely intertwined such that their disruption can have disparate downstream consequences.

Several lines of evidence in *Drosophila* support the notion that sleep deprivation engages different mechanisms from those regulating natural sleep–wake cycles. Baseline sleep and recovery sleep are genetically distinguishable[150], and the neural circuits that regulate baseline sleep are distinct from those that regulate sleep in response to sleep deprivation[151]. Thus, we speculate that the functions of these two sleep states may be distinct.

with the description of sleep in the fruitfly *Drosophila melanogaster*[16,17]. Fruitflies show prolonged immobility during the night, are less responsive to stimulation during their quiescent period and, following forced movement during the sleep period, display immobility during the early day, a time when they are otherwise usually active. These features are reminiscent of mammalian sleep behaviours and responses to sleep loss. Similar to mammals, fruitflies have a clearly defined CNS with a brain, which consists of about 100,000 neurons, and, similar to mammalian sleep, *Drosophila* sleep occurs with an approximately 24-hour circadian periodicity[16,17]. Can animals that lack prominent circadian rhythms sleep? Must a nervous system be a certain size in order for an animal to sleep?

The nematode *Caenorhabditis elegans* has just 302 neurons. The animals develop from fertilized eggs to reproductively mature adults in about 3 days. *C. elegans* sleep during the four transitions between larval stages, in a period called lethargus[20]. During lethargus, which lasts approximately 2 hours[21], the animals stop feeding, reduce their movement and are less responsive to weak stimuli but will still respond to strong stimuli[3,22,23]. Following deprivation of body-movement quiescence during lethargus, the animals show deeper or more quiescence[3,24,25], demonstrating homeostatic regulation of this behaviour. Given its relationship to larval development, sleep during lethargus has been termed developmentally timed sleep[3,26,27]. Therefore, sleep can be found in an animal that has a mere 302 neurons and that lacks overt circadian behavioural rhythms.

Although *C. elegans* does not have a well-defined brain, most neurons are in the front of the animal, thereby forming a CNS of sorts. Can an animal lacking a cephalized nervous system sleep? This question was answered in a recent study of the upside-down jellyfish of the *Cassiopea* genus. *Cassiopea* is in the phylum Cnidaria, a sister group to the bilaterians, which include nematodes, arthropods, molluscs, flatworms and chordates (FIG. 1a). In jellyfish, the body is innervated by nerve nets without a centralized nervous system[28]. The frequency of jellyfish pulsations is higher during the day than during the night. Jellyfish responsiveness is reduced at night and forced movement at night results in reduced activity and reduced responsiveness during the subsequent day, consistent with a homeostatic response[6]. Therefore, jellyfish show sleep behaviour, demonstrating that neither a brain nor a CNS is required for sleep.

Evidence for an ancestral sleep state. Although vertebrates, arthropods, nematodes and Cnidaria species all sleep at a behavioural level, it is possible that the phylogenetic ubiquity of sleep is the result of convergent evolution; that is, sleep could have arisen repeatedly and independently during evolution. However, evidence for conserved neurochemical regulation of sleep in these diverse clades makes this possibility unlikely. For example, the neurotransmitter dopamine suppresses sleep in mice[29], *Drosophila*[30,31] and *C. elegans*[22]. Neuropeptides defined by an amidated arginine-phenylalanine carboxyl-terminus motif (RFamide peptides), which regulate sleep in *C. elegans*[32–34], also regulate sleep in *Drosophila*[35,36] and in the vertebrate zebrafish (*Danio rerio*)[37]. Melatonin promotes sleep in birds[38], fish[1], jellyfish[6] and flatworms[5]. Caffeine and modafinil promote wake in *Drosophila*[17,39] as well as in vertebrates[40,41]. Epidermal growth factor promotes sleep in *Drosophila*[42], mammals[43,44] and nematodes[45]. Finally, sleep deprivation, notwithstanding its limitations as a manipulation for studying sleep function (BOX 1), has been shown in all examined species to induce cell stress, as evidenced by the activation of the endoplasmic reticulum stress response pathway in mammals[46,47], birds[48] and insects[16], and the activation of the FOXO transcription factor in nematodes[25,49]. Thus, it is more parsimonious to posit that sleep existed in a common ancestor than to posit that sleep evolved convergently, each time using the same biochemical regulatory machinery. Moreover, evolutionarily distant species share common sleep functions, including roles in development[26], metabolism[50] and memory consolidation[51]. Taken together, the shared regulatory and functional properties of sleep point to a common ancient origin and may provide a strategy for identifying core functions common across phylogeny (FIG. 1b).

With our current scientific appreciation of the phylogenetic ubiquity of sleep, it would be more contentious to claim that a particular animal never sleeps than to claim that it does. Complicating the search for a non-sleeping animal are the diverse manifestations of sleep across phylogeny. Even among mammals, the variation is profound: sleep time per day ranges from 2 to 3 hours in large herbivores to 20 hours in brown bats[52]. Moreover, certain animals, such as cetaceans[53] and birds[54,55], can greatly curtail sleep time during particular developmental times or seasons. For example, during migration, the white-crowned sparrow *Zonotrichia leucophrys gambelii* sleeps one-third as much as it does when not migrating[55], and the great frigatebird *Fregata minor* spends less than one-tenth of the time sleeping when flying over the ocean as when on land[56]. Newborn killer whales (*Orcinus orca*) and bottlenose dolphins (*Tursiops truncatus*) are thought to be almost continuously active in the first month after birth[53].

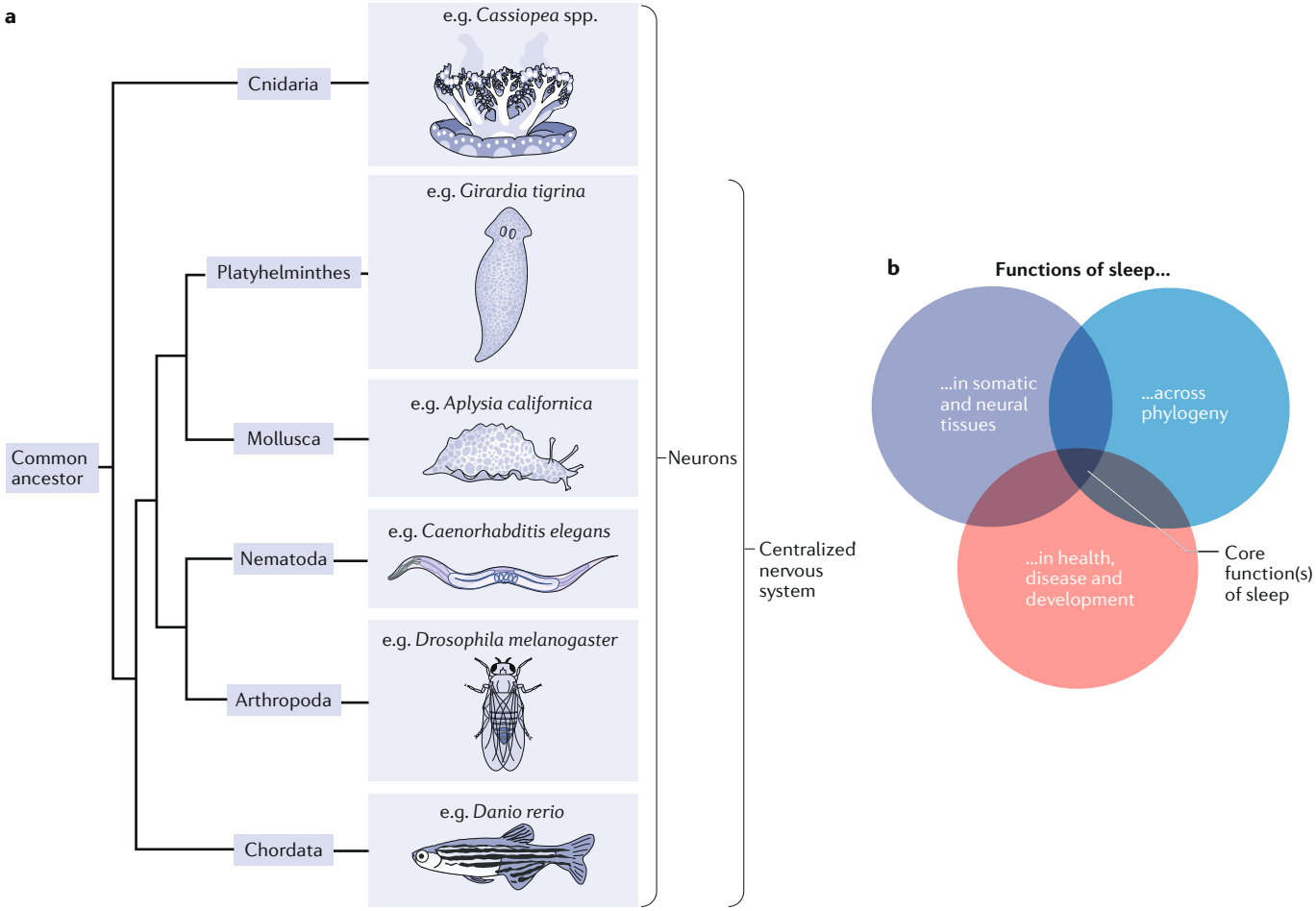

Fig. 1 | **Comparative approach for identifying the core function of sleep. a** | Phylogenetic tree highlighting the six phyla in which sleep has been described. The tree originates (far left) from a common ancestral organism, demonstrating divergent evolution of sleep. Sleep emerged at least 600 million years ago in the last common ancestor to Cnidaria and bilateria. Rapid eye moment (REM) sleep and non-REM sleep have been described only in the phylum Chordata, but behavioural features of sleep are evident across phylogeny, including organisms without centralized nervous systems. **b** | A schematic illustrating the logic of delimiting the core function or functions of sleep by finding functions common to sleep across phylogeny, in neural and non-neural tissue, and during development, sickness and health.

Both migrating birds[56] and cetaceans[57] can show electrophysiological evidence of sleep in one side of the brain while the other side of the brain seems to be awake. Therefore, the burden of proving that an animal does not sleep would require extensive continuous observations during multiple developmental stages and multiple seasons, in multiple environmental conditions and possibly with the use of physiological recordings. Claims of a wholly sleepless animal[58] must be viewed with scepticism.

REM and NREM sleep

Mammalian sleep comes in two electrophysiological and metabolic varieties. Rapid eye movement (REM) sleep is associated with high brain-metabolic demands[59,60] as well as high-frequency EEG activity[61–63], nearly indistinguishable from the demands and activity observed during wakefulness. By contrast, NREM sleep is associated with brain-metabolic demands that are lower than those measured during wakefulness and during REM sleep[59,60]. NREM EEG activity varies depending on sleep depth, but it is generally slower and of higher amplitude than the EEG activity observed during either wake or REM sleep[62]. REM and NREM sleep occur in mammals and birds and may also be present in reptiles[64], suggesting that among vertebrates it was present at least as early as when amniotes evolved more than 300 million years ago.

Was sleep at its nascency more like mammalian NREM or REM sleep? Evidence of lower, slower neural activity in roundworms[23,65], fruitflies[66,67] and crayfish[68] suggests a phylogenetically ancient NREM-like sleep state. However, in roundworms, behavioural sleep is controlled by different mechanisms depending on the context of sleep[69] and, in fruitflies, there are electrophysiological differences between different phases of a single sleep bout[66,70]. Moreover, muscle twitches, which are predominantly observed during REM sleep in young mammals[71], also occur more frequently in juvenile flies than in mature adults[72]. Therefore, whether ancestral sleep was more NREM-like or REM-like remains an unsettled question.

Neural requirements for sleep

The study of sleep has traditionally focused on animals that have brains. Hobson famously wrote that "Sleep is of the brain, by the brain and for the brain"[73]. Sleep regulation in vertebrates[74], *Drosophila*[75] and *C. elegans*[76] is modelled in a top-down manner, with specific neural centres imposing sleep on the rest of the nervous system and then upon the organism at large[74], leading to the suggestion that such neurons are fundamental to all sleeping animals[76].

Table 1 | **Behavioural properties of sleep**

Quiescent behavioural state	Reduced responsiveness?	Rapid reversibility?	Homeostatically regulated?
Sleep[a]	Yes	Yes	Yes
Quiet wakefulness	No	Yes	No
Torpor or hibernation	Yes	No	No
Tonic immobility	No	No	No
Stupor or coma	Yes	No	No
General anaesthesia	Yes	No	No

[a]Sleep is the only state to fulfil all three behavioural criteria; therefore, these behavioural tests have been used to distinguish sleep from other quiescent behavioural states.

Such models of the neural regulation of sleep, coupled with observations of the strong effect of sleep deprivation on human brain function[77] and the use of brain-derived EEG markers as a sleep-defining factor in mammals, have led to the hypothesis that sleep serves a specifically neural function[78,79]. However, intriguing recent experiments have broadened our view of sleep and challenged our preconceptions about its uniquely neural regulation and function.

Brain neurons are top-down regulators of sleep–wake states in mammals, but emerging evidence suggests the contribution of a bottom-up organization. The bottom-up view of sleep posits that as electrical activity of neurons within local neural groups becomes synchronized with the activity of neurons in other local neural groups, behavioural sleep emerges at the organismal level[80,81]. Indeed, in mammalian brains, local neural networks can exhibit slow electrophysiological oscillations (with fewer than four cycles per second) similar to those observed during sleep[81,82] even when the organism is awake. These local sleep-like states are more probable following increased local network neural activity, suggesting that the sleep-like electrophysiological states of these networks serve or reflect a recovery function[81], just as behavioural sleep does for the whole animal. The bottom-up view posits that the local sleep-like state during wake might interfere with the role of the network in normal wake behaviour and is not as effective as organismal sleep at achieving global sleep functions. By contrast, when local neural groups eventually become coordinated, the organism shows sleep behaviour. Whereas the top-down view of sleep and wake is often modelled as a binary switch[83], the bottom-up framework lends itself more naturally to the possibility that sleep and wake lie on a continuum along which the number of local neural groups in the sleep-like electrophysiological state determines the degree of sleepiness of the whole animal. This bottom-up view thus raises an immediate question: what is the smallest quantum of neurons that can generate sleep-like electrical activity?

Primary cultures of rodent cortical neurons exhibit spontaneous electrophysiological and molecular markers consistent with sleep states[84,85]. The neurons show synchronized slow, high-voltage oscillations similar to the slow oscillations observed during NREM sleep in intact animal brains[84]. Treatment of these cortical cultures with wake-promoting chemicals such as noradrenaline or orexin disrupts these slow oscillations and leads to transcriptional changes that are similar to those observed in the brain of intact animals after prolonged wakefulness[84]. These experiments suggest that neither central regulatory neurons nor an intact organism are needed to generate sleep states. In this sense, the neuronal culture experiments provide support for a bottom-up mechanism and potentially explain how sleep could emerge in animals that lack a CNS, such as jellyfish.

Is sleep need driven only by neurons?

Recent experiments suggest that somatic signals contribute to sleep regulation. Mice lacking the core circadian clock gene that encodes brain and muscle ARNT-like factor 1 (BMAL1) exhibit not only aberrant sleep timings but also increased sleep duration[86]. Restoration of *Bmal1* in brain neurons fails to rescue the excessive sleep phenotype in *Bmal1*-deficient animals. Surprisingly, *Bmal1* restoration in skeletal muscle reverses the excessive sleep phenotype of the mutants[87]. Similarly, in *Drosophila*, the NF-κB homologue Relish, which acts in the fat body, an organ analogous to the vertebrate liver, promotes sleep[88]. In *C. elegans*, the metabolically sensitive transcription factor DAF-16 (also known as FOXO) expressed in muscle is required for the increase in sleep amount of certain gene mutants[89] and for the increase in sleep depth after sleep deprivation produced by mechanical stimulation[25] (although evidence suggests that DAF-16 is also active in neurons to promote the homeostatic response to sleep loss[24,89]). The influence of signals from non-neuronal tissues on sleep regulation suggests that the ancestral function of sleep might have resided in non-neuronal cells.

Are neurons necessary for sleep?

Most neurons signal on a timescale of milliseconds to seconds, rapidly sensing and responding to a changing environment. However, sleep and wake are behaviours that occur on a timescale of minutes to hours. Therefore, these states might be controlled by endocrine signals. For example, the chemical melatonin, which is somnogenic in birds[38], fish[1], jellyfish[6] and flatworms[5], is released by neurons that signal via an endocrine mechanism and not via fast synaptic transmission. In *C. elegans*, RFamide neuropeptides are released from a neuron called ALA and signal in an endocrine fashion to regulate sleep[45,90]. We could therefore speculate that non-neuronal cells producing endocrine signals might also be able to influence motor behaviour and reduce sensitivity to external stimuli, resulting in sleep behaviour.

Indeed, it is interesting to consider sleep in animals that lack neurons altogether, such as sponges and the Placozoan species *Trichoplax adhaerens*. *T. adhaerens* have gland cells that are likely to contain and secrete neuropeptides[91]. Despite lacking neurons and muscle, *T. adhaerens* sense and respond to their environment and move and eat via the coordinated action of their cilia[92–94]. Sponges also lack muscles and neurons but carry genes encoding synaptic scaffold proteins[95], can contract coordinately with a diurnal rhythm[96] and can respond to their environment[97]. Evidence that Placozoa spp. or Porifera spp. have a sleep state would demonstrate that sleep is not just for organisms with neurons and would also suggest that non-neuronal cells can organize sleep behaviour.

Even more speculatively, although the search for the simplest sleeping organism has considered only animals, perhaps the search should be expanded to other kingdoms of life. Plants too can move, respond to their environment and show strong circadian rhythms[98]. Many plants synthesize melatonin[99], although its function in plants is not elucidated[100]. *Cassiopea* jellyfish species live in a symbiotic relationship with single-cell photosynthetic algae, which provide carbohydrate fuel to these jellyfish. Do these algae also 'sleep' at night when

photosynthetic activity is absent? Mammals are colonized with intestinal microbiota, the composition of which changes with sleep deprivation[101]. Should these microorganisms be considered to be sleepers? If, at its core, sleep were serving a metabolic function (see below), it is not inconceivable that plants, algae and single-cell prokaryotes will also ultimately be considered to sleep.

Sleep and metabolism

Sleep during development and sickness. In many animals, including humans, there are large changes in sleep amounts and sleep types (REM versus non-REM) during development[26]. In the nematode, sleep is observed during development and coincides with the animal's moult[3], a time of high metabolic demand in the epidermis, which secretes and assembles a new cuticle[20]. In *Drosophila*, sleep occurs during larval stages[102], and sleep quantity and depth are increased in young adult flies compared with mature adult flies[16,103]. In humans and other terrestrial mammals that are born in an underdeveloped state, sleep need is greatest during development[104]. In all these cases, increased sleep is apparently coupled to somatic and neural growth and development.

Mammals, arthropods and nematodes also all sleep more in the setting of either an infectious or non-infectious illness[105]. Sleep seems to be beneficial both for fighting off the infection[106] and for surviving the insult[107,108]. In the case of sickness-induced sleep, the organism's energetic resources are diverted from neural tasks and motor demands to those of fighting and responding to the injurious or infectious insult, consistent with an energy reallocation function of sleep[10].

Sleep–wake cycles as temporal metabolic compartmentalization? Nearly all organisms, ranging from prokaryotes to humans, are subjected to changes in temperature and light conditions over the course of the day. In line with this changing environment, the metabolic requirements of a cell often change with the time of day. An extreme example of this compartmentalization is observed in the photosynthetic cyanobacterium *Synechococcus elongatus*. *Synechococcus* spp. show daily rhythms in nitrogen fixation[109], the process by which the catalytic action of nitrogenase enzyme reduces atmospheric dinitrogen into ammonia[110]. Nitrogenase is inactivated by oxygen; therefore, its activity is incompatible with oxygen produced by photosynthesis. The solution that cyanobacteria evolved to prevent nitrogen fixation and photosynthesis from occurring simultaneously is to express the nitrogenase gene only at night, when photosynthesis does not occur. Remarkably, the transcription of all *Synechococcus* genes varies in a circadian fashion[111], providing an extreme example of temporal compartmentalization of biochemical reactions.

Temporal compartmentalization of metabolism extends beyond circadian rhythms. Budding yeast cells (*Saccharomyces cerevisiae*) do not display overt circadian rhythms in metabolism but do show highly periodic metabolic and transcriptional rhythms[112]. In yeast, DNA replication is restricted to the reductive phase of an approximately 4-hour metabolic cycle, when non-respiratory modes of metabolism are activated, presumably to protect the genome from oxidative damage that could occur during aerobic respiration[113].

With regard to sleep, metabolic temporal compartmentalization may serve not only to separate chemically incompatible reactions but also to divert energetic resources used in neural processing to other uses, whether in the brain or in the body[10]. In addition, the restriction of certain metabolic tasks to the sleep state may facilitate processes with nonlinear energetic demands, as overall metabolic costs may be reduced by restricting such processes to run at high capacity for a limited portion of the day. For example, sleep has been suggested to serve in the clearance of metabolic waste from the mouse brain[114]. The energetic costs for convective clearance are probably insensitive to the amount of solute waste. However, clearance itself might benefit from an economy of scale: the more waste that has been accumulated, the more that can and will be cleared. The animal benefits from packing metabolic clearance into a discrete sleep period. The periodic quiescence and reduced responsiveness that define sleep may reflect the outward manifestation of these synchronized periodic processes in neuronal systems. At the molecular level, the nearest neighbours of sleep and wake may not be other quiescent and active behavioural states but rather cyclic metabolic processes, such as circadian rhythms, the yeast metabolic cycle and the cell cycle. Further descriptions of the metabolic benefits of sleep are summarized in BOX 2.

Once a temporal structure to the schedule of biochemical processes evolved in early animals, other metabolic and behavioural processes may have become optimized for and preferentially attached to a given temporal phase. In this way, the temporal coordination model of sleep predicts not only shared metabolic changes that occur during sleep in different species but also the emergence of numerous tissue-specific and organism-specific molecular changes during both sleep and wake. The molecular changes observed during sleep in various organisms and tissues support this hypothesis. In mammals, the transcriptional response to sleep in the liver, heart and lungs is similar to the transcriptional response in the brain[115–118] and suggests that sleep is a time for anabolic activity and the building of macromolecules in all cell types. Nevertheless, specific molecular changes also vary greatly across tissues and cells. For example, even within the brain, different regions and cell types show unique patterns of sleep-modulated transcription[119]. Moreover, tissue-specific molecular changes that are associated with circadian cycles occur in temporal coordination with sleep and other entrained behaviours such as feeding[117,120]. Indeed, sleep-induced temperature and hormonal changes probably play a part in synchronizing these cycles across the body[121–124]. The connection between sleep and the temporal organization of metabolism is further strengthened by the observations that genes such as *Bmal1* and *Dec2*, which were originally identified for their roles in controlling the circadian orchestration of behaviour and metabolism, also have pronounced effects on sleep and sleep pressure[125].

A theory for sleep function that has received considerable attention in recent years is that sleep evolved to promote neural changes. The strengthening[126] and weakening[127] of neural connections has been reported to occur during sleep, although plasticity of neural circuits and function clearly also occurs during wake[128]. Although such neural processing theories for sleep function are often viewed as alternatives to metabolic theories, they are not necessarily distinct. Sleep-induced savings in neuronal energy[129] and anabolic metabolism[118] may be conducive to neural plasticity. Indeed, the metabolic advantages of sleep may be particularly apparent in the nervous system, which uses a disproportionate share of total body energy[130].

Summary and conclusions

The evolutionary persistence of sleep, in the face of apparent costs of vulnerability to predation and absence of foraging or reproduction, suggests that it has an essential function. Over the past two decades, the phylogenic approach to the study of sleep has taught us much. Although

Box 2 | **Metabolic advantages of sleep**

There are at least four metabolic advantages of sleep. Alternating sleep–wake behavioural states could, conserve energy, temporally segregate chemically incompatible reactions that cannot coexist in the same time and space, coordinate chemically compatible reactions that use the same resources and enhance the efficiency of processes that benefit from economies of scale.

Energy conservation

The simplest metabolic advantage of sleep is the reduction in energetically expensive wake activities, including neural processing and muscle contraction. This adaptive inactivity function of sleep, first proposed by Walker and Berger[7], could explain how total sleep time is influenced by the ecological niches that the animal inhabits. Conservation of energy may also explain the increased sleep observed during prolonged nutrient restriction in rats[152], fruitflies[153] and roundworms[137]. In contrast to the complete absence of nutrients, which results in more sleep, nutrient reduction results in an increase in time used for foraging at the expense of time used for sleep. Such a trade-off between sleep and foraging is observed in cavefish (*Astyanax mexicanus*)[154], *Drosophila*[136,155] and *Caenorhabditis elegans*[156].

Temporal segregation

The yeast metabolic cycle segregates oxidative reactions from reductive reactions and anabolic reactions from catabolic ones[112]; a biochemical milieu that favours one set of reactions would impede others. Similarly, transcriptomic[118] and proteomic data[157,158] from asleep and awake animals suggest these to be periods of relative macromolecular synthesis and degradation, respectively, probably requiring different chemical environments.

Resource coordination

Energy reallocation during sleep is an example of metabolic coordination. The brain and body can each synthesize macromolecules, but a limited budget of energy and chemical supplies may preclude synthesis in all tissues simultaneously. Although the total rate of energy expenditure may remain static, sleep may shift energy utilization away from wake-related processes towards other areas of need, both in neural and non-neural cells[10]. Metabolic coordination is distinct from the proposed 'adaptive inactivity' function of sleep[7,159] in the sense that energetic resources are not necessarily saved during sleep; rather, they are used for different functions during sleep than during wake[10].

Energetic efficiency

Processes with fixed metabolic costs are more efficient when active for a shorter time but at higher capacity. Recent work on the mammalian glymphatic system, for example, suggests that sleep facilitates bulk cerebrospinal fluid transport and the clearance of toxic metabolites[114]. The energetic costs of bulk convection are largely independent of metabolite concentrations; thus, it is more efficient to wait for metabolic waste to 'build up' before engaging in an expensive new round of convective clearance.

Ultimately, the emergence of distinct sleep–wake states for any of the above metabolic advantages will influence the temporal availability of enzymes, substrates and energy sources. Reactions that use these cellular resources may therefore become more efficient at specific times or states. Regulatory systems that enforce the cycling of these connected reactions may offer a metabolic advantage. In this way, the emergence of metabolic oscillations has the potential to spread, influencing global metabolic structure and conferring evolutionary stability to distinct sleep and wake states.

sleep has been described in just 6 of the 36 known phyla, the preponderance of evidence supports the idea that sleep emerged early in animal evolution[131]. Studies on the molecular changes associated with sleep in different tissues and in vitro continue to provide insights into sleep function and regulation. These data point to metabolic demands as a key driver of sleep regulation and to sleep itself as serving primarily metabolic roles.

The study of sleep is both informed and limited by its definition. To date, identifying sleep has relied on behavioural criteria, and this behavioural definition has taken us far, enabling us to study sleep in various species and conditions. Yet, as we move outward on the phylogenic tree, this definition will continue to be tested. Is the transient absence of motor activity the sine qua non of sleep? Can generally sessile animals, such as sponges, sleep? Must reduced responsiveness be exhibited for some specific sensory stimuli? If somatic cells, for example, demonstrate periodic and homeostatically guarded reductions in their molecular responsiveness to receptor activation, does this count as sleep? Once the essential function of sleep is understood, it may come to be appreciated in organisms that lack the behavioural features that once defined it. We envision that future advances will feed back on our understanding and definition of sleep. In this 'omics' era, we are well poised to identify molecular signatures that mark sleep. Indeed, if the metabolic function model is correct, metabolomics may be the natural tool to use to study sleep[132–134]. It is likely that in the future, we can add more specific biochemical or molecular parameters to our definition of sleep.

If sleep is at its core a metabolic state, then one would expect genetic or pharmacological manipulations of metabolism to have effects on sleep. In this vein, it is interesting to note that several genes that affect both metabolism and sleep have been identified in mammals[86], *Drosophila*[135,136] and *C. elegans*[25,137]. We predict that future comprehensive searches for sleep-regulating genes should identify a disproportionately high number of genes known to function in metabolism. Such analyses should be soon forthcoming, as they are now feasible in powerful invertebrate model systems such as *Drosophila* and *C. elegans*.

The debate as to the function of sleep continues. The growing body of data describing sleep and sleep regulation across the tree of life, throughout neural and non-neural tissues and in vitro, is forcing us to rethink the nature of sleep. Later in Shakespeare's *Macbeth*, Lady Macbeth calls sleep "the season of all natures". It may be that the essential feature in the "Chief nourisher in life's feast" is not a yet-unappreciated gene or metabolite but a temporal structure and organizational principle for coping with the energetic and chemical demands of life, given the constraints of time and space.

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https://doi.org/10.1038/s41583-018-0098-9

Published online: 20 December 2018

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Acknowledgements
The authors thank A. Rohacek and S. Belfer for comments. R.C.A. is supported by US Defense Advanced Research Projects Agency grant D17AP00003; M.S.K. is supported by K08NS090461 (US National Institutes of Health), a Burroughs Wellcome Career Award for Medical Scientists, a March of Dimes Basil O'Connor Scholar Award and a Sloan Research Fellowship; and D.M.R. is supported by R01NS088432 (US National Institutes of Health).

Author contributions
All authors wrote the manuscript.

Competing interests
The authors declare no competing interests.

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Reviewer information
Nature Reviews Neuroscience thanks D. Prober, M. Zimmer and the other anonymous reviewer(s) for their contribution to the peer review of this work.