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REVIEW

CENTENARY ARTICLE

Comparative biology of sleep in diverse animals

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ABSTRACT

Sleep is a familiar, periodic occurrence in our lives. Despite its place in everyday experience, the existence of this suspended state of consciousness has intrigued and puzzled philosophers and scientists for decades. For much of its history, sleep science has focused on humans and mammals. In contrast, in the last 20 years or so, it has become increasingly clear that sleep is essentially universal. Sleep states have been observed in animals from mammals to cnidaria. Here, we review recent progress in sleep science through the lens of comparative physiology. We highlight broad insights into sleep phenomenology, physiology and function that have come from this comparative approach. These include the plasticity of sleep in response to environmental challenges and ecological niches, the discovery of distinct sleep stages in diverse taxa and conserved functions of sleep. Indeed, we argue, a comparative approach is essential to any comprehensive account of sleep.

KEY WORDS: Sleep, Evolution, Phylogeny, Sleep plasticity

Introduction

As a state we enter into and exit from daily, sleep is a familiar occurrence in our lives. The perceptual disengagement associated with sleep though has possibly had the unfortunate side effect of leading our thinking on sleep astray in important ways. Historically, sleep has been viewed as merely a passive interruption of the waking state (Kleitman, 1963). Further, as the experience of consciousness is so particular to humans, we believe that a human- and mammalian-centric view of sleep has developed.

Both of these views have been challenged by modern sleep science. Sleep is now generally accepted as an active state (Aserinsky and Kleitman, 1955; Aserinsky and Kleitman, 1953; Moruzzi and Magoun, 1949; Wilson and McNaughton, 1994). Moreover, although initially seen as a largely mammalian phenomenon, sleep is now recognised to be a near-universal feature in animals (Fig. 1). Sleep states have been reported in nearly every class of animals with a nervous system – from mammals with large brains, such as dolphins and elephants (Gravett et al., 2017; Tobler, 1992; Williams et al., 2015; Lyamin et al., 2005; Mukhametov et al., 1977), to cnidarians with nerve nets, such as jellyfish and hydra (Nath et al., 2017; Kanaya et al., 2020).

Comparative biology, of which comparative sleep research is a particular example (Anafi et al., 2019; Keene and Duboue, 2018; Lesku et al., 2009), aims to look across all taxa to try and uncover general principles. Initial efforts towards understanding common principles of sleep involved comparative analyses of sleep duration across taxa (Capellini et al., 2008; Lesku et al., 2008). These efforts yielded somewhat mixed results, complicated by the unequal representation of different taxonomic groups and by the fact that sleep duration is modifiable by seasons and rearing conditions (captivity versus in the wild), amongst other factors (Rattenborg et al., 2008; Voirin et al., 2014; Davimes et al., 2018). Indeed, there is great diversity in sleep observed across taxa. This sleep plasticity is widely prevalent, yet has not received much attention. In this Review, we will examine sleep in different taxa with a particular focus on invertebrates. Although most animals are invertebrates, invertebrate sleep has historically not received as much attention as sleep in vertebrates. We will start with a discussion of the criteria used to define sleep, discuss the striking plasticity of sleep and then highlight insights into sleep physiology and function that have come from studying diverse animals.

Definition of sleep

Perhaps the first systematic enumeration of criteria to define a sleep state was from Pieron (1913), who defined sleep using behavioural criteria. More recently, sleep has been defined using either changes in electrical activity as typified by electroencephalogram (EEG) signatures or behavioural criteria. There are four behavioural criteria that are well accepted (Campbell and Tobler, 1984) to characterise a quiescent state as sleep. First, sleep is a period of immobility. Second, the quiescence must be rapidly reversible. This distinguishes sleep from states such as coma, anaesthesia, torpor and hibernation. Third, the sleep state is associated with increased arousal thresholds. This is an important criterion as it distinguishes sleep from quiet wakefulness. Fourth, sleep is homeostatically regulated, i.e. a period of sleep deprivation is expected to be followed by a rebound of increased sleep amount or depth or both. In addition to these four criteria, animals in sleep frequently adopt a sleep-specific posture and sleep in specific sites.

These criteria are now well established and have been used to define sleep states in a range of different animals (Table S1). When applying these criteria to define sleep, however, some caution is warranted. These criteria by themselves do not unambiguously define a sleep state. For example, sleep states are not always associated with immobility: humans frequently twitch during non-rapid eye movement (NREM) sleep (Sullivan et al., 2022), dolphins and fur seals can sleep while swimming and some birds sleep in flight (Rattenborg et al., 2016). Homeostatic responses to sleep loss are also frequently variable. There are numerous examples in the literature of animals exhibiting very little to no rebound following a period of sleep loss (Gravett et al., 2017; Lyamin et al., 2005; Loftus et al., 2022). We will discuss these phenomena in a little more depth in the next section on sleep plasticity. Arousal thresholds, although certainly generally elevated in sleep, are also clearly modality specific and dependent on the salience of the arousing stimulus (Oswald et al., 1960). This can be seen in the common example of a mother awakening to a child's name or cry, or people awakening more readily to their own name (Oswald et al., 1960). EEG signatures too are not by themselves deterministic of sleep. As

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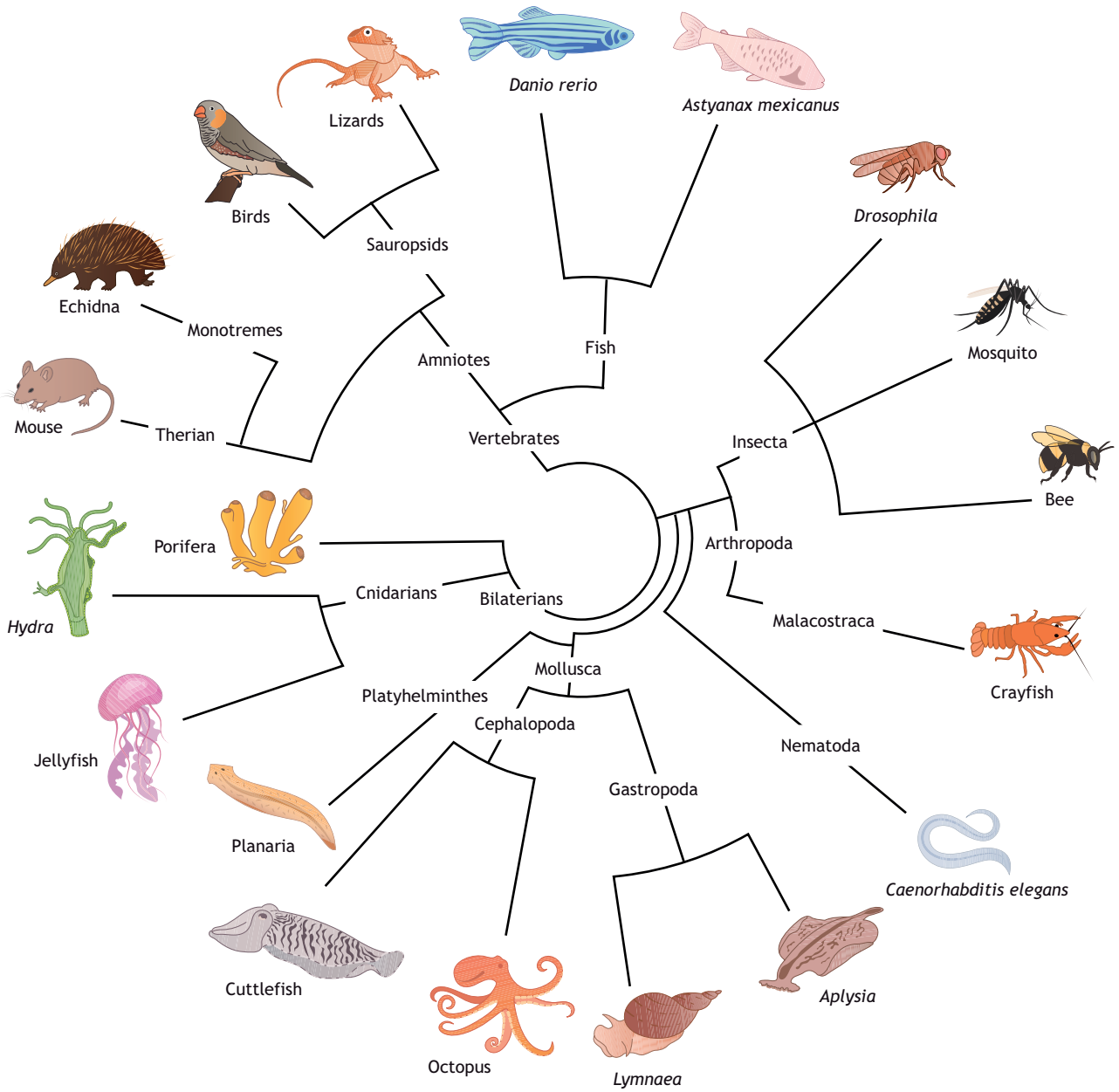

Fig. 1. A circle of life depicting animal models used in sleep studies. Branches depict evolutionary relationships (Cannon et al., 2016), but branch lengths are not intended to represent evolutionary distance. Figure redrawn based on Keene and Duboue (2018).

detailed in Box 1, in rapid eye movement (REM) sleep, the EEG is characterised by wake-like signatures of desynchronised low-voltage activity. Conversely, sleep-like EEG patterns in awake animals are seen following administration of various pharmacological agents (Wikler, 1952; Bradley and Elkes, 1953). The farther we go along the tree of life from humans, the more EEGs – and neural activity signatures more broadly – might be different from our own and, thus, the less useful they are for defining sleep.

Collectively, these behavioural criteria have been used to define sleep slates across taxa (Shaw et al., 2000; Hendricks et al., 2000; Vorster et al., 2014; Raizen et al., 2008; Nath et al., 2017; Prober et al., 2006; Frank et al., 2012; Medeiros et al., 2021; Kanaya et al., 2020; Stephenson and Lewis, 2011; Zhdanova et al., 2001). It is our view that the field would particularly benefit from a careful, precise and sensitive measurement of arousal thresholds to define the sleep state and also to get some measure of sleep depth. Indeed, in humans, changes in EEG slow-wave activity (SWA; Box 1) correlate well with changes in arousal thresholds following sleep loss, and changes in arousal thresholds track the progression of sleep stages through the sleep cycle (Pisano et al., 1966; Rechtschaffen et al., 1966). Unfortunately, as detailed in Table S1, a sensitive measurement of arousal thresholds has not been universally applied.

In Table S1, we tabulate the criteria used to characterise sleep states in different species, with a particular focus on invertebrates and novel reports of sleep in the last 20 years. Although satisfying the four behavioural criteria is sufficient to define a sleep state, we find that, frequently, investigators go above and beyond these minimally sufficient criteria. Similarities reported include pharmacological parallels, ontogenetic (i.e. age-dependent) changes and, crucially, measurements of sleep function. Indeed,

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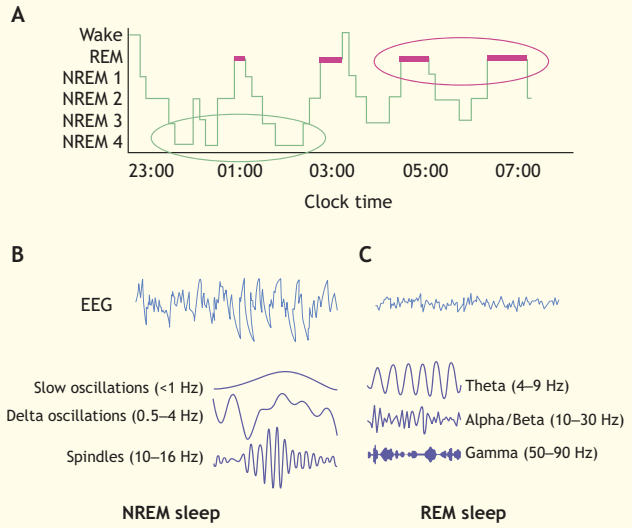
Box 1. Oscillatory activity in different sleep states

In young adult humans, sleep through the night is characterised by a cyclic alternation between NREM and REM sleep states. These are defined by their characteristic neural activity signatures as measured by oscillations in the electroencephalogram (EEG) and concomitant changes in arousal thresholds. Sleep in the early night consists of proportionately more NREM sleep, with the proportion of REM sleep (pink bars) increasing through the night as seen in the hypnogram in A, a hypnogram of sleep stage distribution in a young adult (adapted from Melnattur, 2023). The sleep periods in the early night are predominantly of NREM sleep (green ovals in A). In contrast, the sleep periods at the end of the night are predominantly of REM sleep (pink ovals in A). These topics have been previously reviewed in depth (Sullivan et al., 2022; Adamantidis et al., 2019) so we will be brief in our coverage.

Stage 3 and 4 NREM sleep are together referred to as slow-wave sleep (SWS) or 'deep sleep', as arousal thresholds are higher than in stage 1 and 2 NREM sleep. The EEG patterns in this stage (B) are typified by the eponymous high-amplitude slow oscillations (<1 Hz). The upper trace in B shows a representative EEG from SWS, and the component frequencies are shown below. Slow oscillations have their origin in the cortex, and result from synchronised alternation between a hyperpolarised 'down' state and a depolarised, burst firing 'up' state. Also present are so-called delta waves (0.5–4 Hz) and sleep spindles. Power in the delta frequency mirrors changes in sleep pressure. Spindles, so called as the pattern of oscillation resembles a spindle, are transient oscillations in the 10–16 Hz range. They have their origin in the thalamus, and can be waxing or waning (in amplitude). Spindles are also present in stage 2 NREM sleep.

In contrast to NREM sleep, the EEG signal in REM sleep is typified by low-amplitude, desynchronised, mixed high-frequency firing (C). The upper trace in C shows a representative EEG from REM sleep with its component frequencies below (based on data from Adamantidis et al., 2019). The component frequencies are in the theta (4–9 Hz), alpha/beta (10–30 Hz) and gamma (50–90 Hz) range.



the pioneering studies that reported sleep in the fly *Drosophila* (Shaw et al., 2000; Hendricks et al., 2000) showed that fly sleep met these four criteria and several others. Flies exhibit ontogenetic changes in sleep that parallel those seen in humans – young flies sleep a lot, whereas aged flies show sleep deficits. Pharmacological compounds modulate sleep similarly in flies and humans – caffeine promotes waking, antihistamines make flies drowsy. Finally, homologous genes have been identified that are similarly modulated by sleep and wakefulness in flies and mammals (Shaw et al., 2000). Subsequent work identified electrophysiological and respiratory changes during sleep in flies that mimicked those in mammals (Nitz et al., 2002; Stahl et al., 2017), and sleep in flies was shown to support similar functions in flies and mammals, including memory and cognition (Bushey et al., 2011; Cirelli et al., 2005; Seugnet et al., 2008; Dissel et al., 2015a; Donlea et al., 2011; Ganguly-Fitzgerald et al., 2006; Melnattur et al., 2021; Chouhan et al., 2021) and – as detailed in the following sections – clearance, i.e. removal of toxic metabolites (van Alphen et al., 2021).

The report that introduced the most recent entrant into the group of animals known to sleep – the cnidarian *Hydra* – is also worth considering in this regard (Kanaya et al., 2020). Kanaya and colleagues (2020) showed though video analysis that *Hydra* exhibit periodic quiescent bouts. These quiescent episodes are reversible by bright light at night. Further, *Hydra* immobile for >20 min exhibit elevated arousal thresholds to light pulses, leading to the definition of 20 min of immobility as a sleep bout in *Hydra*. Mechanical sleep deprivation at night induces a rebound in sleep the next day. *Hydra* sleep thus meets all four established behavioural criteria for sleep. The authors subsequently demonstrated that melatonin and GABA (see Box 2) promote sleep in *Hydra* as they do in mammals. Gene profiling identified genes modulated by sleep and wakefulness in *Hydra*. These genes were knocked down in *Drosophila* and shown to similarly change sleep and wakefulness in flies. Finally, sleep deprivation in *Hydra* affects development and cell proliferation (Kanaya et al., 2020).

In the absence of a description of sleep at a cellular or molecular level, scientists rely on correlates of sleep for their analyses. Therefore, the more correlates we have of sleep, the more readily a new report of sleep would be accepted by the community. Detailed mechanistic analyses of sleep are obviously far easier in model organisms in a laboratory than in animals in the wild, but even investigations into sleep in natural settings might benefit from studying how sleep states are modified under different circumstances.

Finally, it is important to keep in mind some caveats about inferring evolutionary relationships from comparative analyses of sleep. Sleep can, of course, only be measured in extant species. Similarities between distantly related species could result from conserved phenomena, or from convergent evolution. To distinguish between these possibilities, it will help to analyse multiple examples from each taxon.

Sleep plasticity

In the last 20 years, technological advances have allowed sleep research to move out of the laboratory into the wild (Rattenborg et al., 2017). These advances have enabled the study of sleep in more animals than would be possible otherwise. They have also provided compelling evidence that sleep itself is plastic and modifiable in response to ecological niches that species inhabit, and environmental challenges that individual animals encounter in their lifetimes. Here, we consider some interesting and striking examples of sleep plasticity in response to ecological factors and highlight insights into potential mechanisms underlying these effects. The magnitude of the effects reported is often large, and sleep plasticity appears to be widespread. Understanding sleep plasticity is thus an important part of understanding the neural control of sleep.

Sleep in captivity and in the wild

Since the study of sleep in the wild has become technically feasible, it has become clear that the sleep of animals in the wild can be quite different from sleep in captivity. The first report of EEG recordings

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Box 2. Neurotransmitter systems regulating sleep and wakefulness

In the mammalian brain, sleep and wake regulatory circuits are distributed throughout the neuraxis, and they express distinct neurotransmitters. Here, we briefly highlight a few arousal- and sleep-promoting transmitter systems; these have been more extensively reviewed elsewhere (Liu and Dan, 2019; Scammell et al., 2017).

In mammals, the peptide hypocretin/orexin secreted from the lateral hypothalamus is a potent arousal-promoting compound. Orexinergic neurons project widely in the brain, and excite other arousal-promoting centres while inhibiting sleep-promoting centres. Loss of orexinergic neurons in humans is thought to underlie narcolepsy, a sleep disorder characterised by an inability to maintain a waking state (Lin et al., 1999; Peyron et al., 2000). The neurotransmitter dopamine also plays a role in promoting arousal that is well known and well conserved. Many stimulants, e.g. modafinil and amphetamines, appear to function through dopaminergic modulation (Qu et al., 2008; Wisor et al., 2001; Spencer et al., 2015). In the mammalian brain, dopaminergic neurons in the ventral tegmental area are the key arousal-promoting dopaminergic nucleus. Other monoaminergic systems including serotonin, histamine and noradrenaline (norepinephrine) also promote arousal (Scammell et al., 2017). Interestingly, in *Hydra*, dopamine appears to be sleep promoting (Kanaya et al., 2020).

The best characterised sleep-promoting transmitter system is perhaps gamma amino butyric acid (GABA). Many sedatives (e.g. benzodiazepines) function through GABA receptors (McKernan et al., 2000). In the mammalian brain, the major GABAergic nuclei are in the ventrolateral preoptic nucleus (VLPO) and the parafacial zone (Anaclet et al., 2014; Sherin et al., 1996). The VLPO GABAergic neurons inhibit and are, in turn, inhibited by arousal-promoting systems, constituting a 'flip-flop' switch that enables rapid transitions between states (Saper et al., 2010). The sleep-promoting role of GABA also extends to *Drosophila* and *Hydra* (Donlea et al., 2011; Pimentel et al., 2016; Ni et al., 2019; Kanaya et al., 2020). Another molecule with a mild sleep-promoting role in humans is melatonin, secreted from the pineal gland. It is the output hormone of the circadian clock. Indeed, melatonin supplements are frequently used to treat symptoms of jet-lag.

from unrestrained animals in the wild was obtained from the three-toed sloth (*Bradypus variegatus*) in a tropical rainforest (Rattenborg et al., 2008). Sloths in the wild sleep for about 9.5 h a day, a figure approximately 6 h less than that reported for sloths in captivity (De Moura Filho et al., 1983). Similarly, elephants in captivity were reported to sleep for about 4–5 h, whereas elephants in the wild only sleep about 2 h on average (Gravett et al., 2017; Tobler, 1992; Williams et al., 2015). A recent study from Kendall-Bar et al. (2023) reported similar phenomena in the elephant seal (*Mirounga angustirostris*). Elephant seals in the wild were found to sleep ∼10 h a day on land, and only ∼2 h a day while at sea on foraging trips. This reduction in sleep was much more dramatic than the modest reductions seen for sleep in water versus land for seals in laboratory settings (Lyamin et al., 2018; Kendall-Bar et al., 2023). Pressures that might drive sleep suppression in the wild include a need to forage for food as opposed to being fed *ad libitum* in captivity, and a presumably greater predation risk.

A recent report from Loftus et al. (2022) studying olive baboons (*Papio anubis*) supported and extended these findings to the study of sleep homeostasis. Baboons were found to sleep less when in unfamiliar sites, and when surrounded by their group mates. This was unaffected by their prior sleep history and, crucially, there was no observed rebound in sleep amount or depth following a period of sleep loss. These results show that sleep and sleep drive are clearly plastic.

Starvation and foraging

Sleep suppression by starvation has been well documented in mammals (Jacobs and McGinty, 1971; Roky et al., 2003). This response is thought to be an evolutionary adaptation to help animals forage for food. Similar phenomena have been observed in the nematode *Caenorhabditis elegans*, the fly *Drosophila* and the Mexican cavefish *Astyanax* (Goetting et al., 2018; Duboué et al., 2011; Jaggard et al., 2018; Keene et al., 2010; Yurgel et al., 2019; Thimgan et al., 2010).

Drosophila starved for 24 h robustly suppress sleep (Keene et al., 2010; Thimgan et al., 2010). Following this period of starvation-induced sleep loss, no rebound was observed, and flies retained the ability to learn (Thimgan et al., 2010). As detailed below, sleep loss and extended waking impairs learning and memory in a range of animals (Dissel et al., 2015b; Brodt et al., 2023). Starvation-induced waking thus appears to be somewhat distinct from other kinds of waking. Subsequent work has begun to unravel the molecular and neural circuit underpinnings of these phenomena. Starvation-induced sleep suppression was shown to depend on the release of the neuropeptide leucokinin (lk) from a single pair of neurons onto insulin-producing cells (IPCs) (Murakami et al., 2016; Yurgel et al., 2019). Activity of these lk-expressing neurons increases in the starved state (Yurgel et al., 2019). Further, mutations in lk or the leucokinin receptor result in increased levels of insulin-like peptides (Zandawala et al., 2018). Consistent with these findings, loss-of-function mutations in insulin-like peptides (Ilps) reduce sleep, and overexpression of Ilps increases sleep (Cong et al., 2015).

The Mexican cavefish *Astyanax mexicanus* has cave- and surface-dwelling forms. The cave-dwelling populations are eyeless and exhibit dramatic reductions in sleep relative to their surface-dwelling counterparts (Duboué et al., 2011). Signalling mediated by the conserved neuropeptide hypocretin from the fish lateral line was shown to underlie sleep loss in the cave-dwelling forms (Jaggard et al., 2018). Thus, animals can apparently dispense with sleep under certain circumstances. Work in *Drosophila and Astyanax* – one a classic laboratory model, the other an intriguing emerging model organism – have yielded important insights.

Mating and sexual arousal

A remarkable example of animals dispensing with sleep comes from a study of pectoral sandpipers, *Calidris melanotos* (Lesku et al., 2012). These birds breed in the Arctic tundra in regions that experience constant daylight during their weeks-long mating season. Male sandpipers are polygynous. Their reproductive success is thus dependent on finding as many potential female mates as possible. Conversely, females must find the best mate to sire the sole clutch of the year. There is thus intense competition among male sandpipers for females. Males spend much of the season fighting other males in competition for females and for territory. Lesku et al. (2012) found that some males could almost entirely dispense with sleep for weeks without suffering much in the way of consequences. One male sandpiper was active >95% of the time for 19 days consecutively. Remarkably, the males that sired the most offspring included some of those that slept the least and had the most fragmented sleep (Lesku et al., 2012). These results are particularly surprising, as they fly in the face of sleep being critical for evolutionary fitness.

As with sandpipers, *Drosophila* males too dramatically reduce sleep in sexual contexts (Beckwith et al., 2017; Machado et al., 2017; Chen et al., 2017). Male flies suppress night-time sleep when paired with females. They also do not seem to make up for the sleep

lost with a rebound on the following day, despite male flies apparently still accumulating sleep pressure, i.e. sleep drive. Further, female pheromones also suppress rebound sleep in response to mechanical sleep deprivation. The effects of sexual arousal on sleep are mediated by specific pheromone-sensing neurons in the peripheral nervous system and central brain neurons (Beckwith et al., 2017; Machado et al., 2017; Chen et al., 2017).

Migration

Many animals migrate large distances seasonally, often remaining on the move for several days, a state that would seem to be incompatible with sleep. Indeed, studies in migratory birds largely substantiate these ideas (Rattenborg et al., 2004, 2016). Using EEG measurements on captive birds during the migratory season, white-crowned sparrows (*Zonotrichia leucophrys gambelii*) were shown to spend about two-thirds less time in sleep than in the non-migratory season. Despite losing sleep, their accuracy in an operant repeated acquisition task remained at a high level. In contrast, sleep restriction impaired performance in the same birds in the non-migratory season (Rattenborg et al., 2004). Thus, despite losing sleep, the birds were able to carry out some sleep functions, i.e. retaining accuracy in cognitive performance as measured using this repeated acquisition task.

The first study to monitor the sleep of birds in flight used EEG data loggers to record the sleep of great frigatebirds (Rattenborg et al., 2016). These birds take long flight paths where they remain in flight for up to a week. Rattenborg and colleagues (2016) found that these birds do sleep while in flight. Sleep in flight is usually unihemispheric (wherein half of the brain can exhibit slow waves whereas the other half of the brain is awake and vigilant), but is also occasionally bihemispheric. However, great frigatebirds drastically reduce their sleep time – sleeping an average of about 40 min per day while in flight for 6 days, as opposed to approximately 12 h per day while on land. Sleep occurs when birds are soaring in circles on rising air currents, but has never been observed in flapping flight (Rattenborg et al., 2016).

Of course, it is not just birds that migrate. Gravett et al. (2017) used trunk accelerometery data to monitor the sleep of two African elephant (*Loxodonta africana*) matriarchs. They found that the two observed elephant matriarchs could spend a couple of days migrating from one site to another and could go without sleep altogether for up to 46 h. No rebound was observed following this period of sleep loss (Gravett et al., 2017).

Caring for young

In many animals, from mammals to flies, sleep duration is highest in early life. Sleep loss in early life is associated with many long-lasting consequences (Seugnet et al., 2011; Kayser et al., 2014). Given the well-established importance of sleep in early life, the findings of Lyamin et al. (2005) were especially surprising and striking. They monitored sleep of killer whales (*Orcinus orca*) and dolphins (*Tursiops truncatus*) around the time of birth and found that both the mother and the calf remained continuously active for weeks to months following birth. In natural settings, the mother and the new-born calves migrate together over large distances to feeding grounds. This is a period where they could be under risk of predation and thus might need to maintain vigilance. These findings have generated vigorous debate in the community, with other groups suggesting alternative interpretations (Gnone et al., 2006; Sekiguchi et al., 2006). That said, the fact that sleep is apparently dispensable in these animals at what is thought to be a critical time is still very intriguing.

Interestingly, the phenomenon of giving up sleep to care for young is also observed in a social insect – the bumble bee (*Bombus terrestris*) (Nagari et al., 2019). By video recording isolated worker bees, Nagari et al. (2019) found that bees reduce sleep in the presence of larvae, which need to be fed, and pupae, which do not. Empty cocoons from which pupae had been removed also elicited sleep suppression, suggesting that this effect might be mediated by pheromone signals. These findings in bees are especially interesting as they suggest that animals can suppress sleep to care for the young of the brood that are not their own.

Maintaining vigilance

As mentioned above, birds (and some marine mammals) are capable of unihemispheric and asymmetric NREM sleep (sometimes also called unihemispheric slow-wave sleep or USWS). In a remarkable study, Rattenborg et al. (1999) and colleagues showed that birds can modulate the occurrence of USWS in response to the threat of predation. Video recordings of sleep behaviour were arranged with mallard ducks (*Anas platyrhynchos*), lined up in a row. Closure of one eye indicated USWS, whereas closure of both eyes suggested bihemispheric slow-wave sleep (SWS) or REM sleep. The ducks at the end of the row (the edge of the group) were much more likely to use USWS than those in the middle. Further, the ducks at the edge also directed their open eye away from the group (Rattenborg et al., 1999). Keeping one eye open presumably allows mallards in a potentially vulnerable location to remain vigilant to the threat of predation.

More recently, Kelly et al. (2015) observed a similar phenomenon of unilateral eye closure (UEC) with crocodiles (*Crocodylus porosus*). Juvenile saltwater crocodiles were individually housed in a Plexiglas enclosure. Upon exposure to a human stimulus, crocodiles were found to increase their time spent in UEC, and to direct the open eye towards the intruder. Crocodiles also similarly directed their open eye towards conspecifics (Kelly et al., 2015).

These studies suggest that animals sleep more lightly when faced with the threat of predation. Other reports, however, suggest a more nuanced picture. Voirin et al. (2014) studied sleep in two species of sloths in the Panamanian rainforest – one on the mainland (*Bradypus variegatus*; exposed to predation) and one on an island (*Bradypus pygmaeus*; safe from predation). Although sleep duration at the two sites was comparable, the mainland sloths slept mainly at night (a time when their predators were active). Similar results were seen in a study of Norwegian rats (*Rattus norvegicus*) in middens, where they were under risk of predation (Fenn and Macdonald, 1995). These normally nocturnal rats changed their sleep patterns to become diurnal when under predation by foxes, which are also nocturnal. Although these results might at first seem to be at odds with the reports above, it is worth keeping in mind that animals in the wild typically sleep in safe sites. When compelled to be in exposed sites, animals might sleep more lightly, but might choose to spend the night in a familiar safe location when they have access to it (Tisdale et al., 2018; Ferretti et al., 2019).

These reports of ecological factors driving sleep can feel esoteric, like quirks of evolution. An interesting recent study in humans on the so-called ‘first-night effect’ of sleep recordings in a sleep laboratory is worth considering in this regard. Tamaki et al. (2016) found that humans too can exhibit asymmetries in SWS in unfamiliar surroundings (such as a sleep laboratory), where some vigilance might be warranted. To monitor sleep, the authors used both EEG and magnetoencephalogy (MEG) – a technique used to measure neural activity-generated magnetic fields in the scalp.

MEG recordings revealed an asymmetry in SWA on the first night in a novel environment (the sleep laboratory). This SWA asymmetry was mirrored by an increased responsiveness to 'oddball' tones, suggesting an asymmetry in alertness as well (Tamaki et al., 2016). The study of sleep in ducks in a row, at first seemingly esoteric, thus found a surprising application in human sleep science.

Sensory inputs driving sleep plasticity

The cases we have considered so far are all examples of adaptive sleep loss and suggest that animals can dispense with sleep under certain circumstances. However, there are numerous examples of plastic increases in sleep. Learning for example, increases sleep in many animals (Moroni et al., 2008; Eschenko et al., 2008; Oliva et al., 2020; Ganguly-Fitzgerald et al., 2006). In this subsection, we consider a couple of recent *Drosophila* studies that provide evidence of plastic increases in sleep, of which some were somewhat unexpected. They are also interesting examples of peripheral sensory inputs that can drive sleep and sleep plasticity.

Experimental studies in humans have confirmed anecdotal observations that rocking increases sleep and sleep-related oscillations in humans (Bayer et al., 2011; Perrault et al., 2019). Two recent studies in *Drosophila* showed that rocking and gentle vibration can increase sleep in flies, too (Öztürk-Çolak et al., 2020; Lone et al., 2021). Both groups found that rocking-induced sleep was dependent on peripheral mechanosensory neurons in the fly's antenna that express the nanchung channel.

Moreover, Melnattur et al. (2020) made the surprising discovery that disrupting flight increases sleep. Further, they identified a specific neural pathway from wing chemosensory neurons to the brain that mediates this effect. Melnattur et al. (2020) suggest that, because wing damage is a common occurrence in a fly's life (Davis et al., 2018), flies may have evolved this mechanism to enable them to adapt their behaviours to a commonly encountered circumstance (Gorostiza et al., 2016).

The classical view of sleep is that sleep results exclusively from 'internal necessity' and not from external conditions (Pieron, 1913). In contrast, these studies and other recent work (Kompotis et al., 2019; Seidner et al., 2015) suggest that peripheral sensory inputs are powerful modulators of sleep and sleep drive.

Sleep stages

The development of all-night continuous sleep recording in humans led to the characterisation of different sleep stages (Dement and Kleitman, 1957). The canonical picture of sleep stages has been of a cyclic alternation between NREM sleep, characterised by high-amplitude slow waves and spindles, and REM sleep, characterised by low-amplitude high-frequency wake-like signals in the EEG (see Box 1; Sullivan et al., 2022). This was thought to be universal among mammals and unique to mammals and birds. However, as sleep states have been investigated in more animals, this view has been challenged. Here, we review recent developments on the characterisation of sleep stages in marine mammals, monotremes, reptiles, fish and invertebrates.

Marine mammals

In contrast to terrestrial mammals, which have bihemispheric symmetric sleep, cetaceans exhibit USWS (Mukhametov et al., 1977). USWS often occurs while the animal is swimming. There does not appear to be any asymmetry in motor activity while the animals are in USWS, and asymmetry in arousal thresholds has not been investigated. Motor activity and sensory responses in USWS must therefore differ from bihemispheric SWS. USWS is thus a different state from SWS in land mammals. Further, cetaceans do not apparently exhibit EEG signatures of REM sleep (Mukhametov et al., 1977). Although cetaceans have been reported to exhibit some behavioural signs of REM sleep, it has been hard to unambiguously identify these as being associated with REM sleep (Lyamin et al., 2008).

Animals that are part terrestrial and part marine, such as the fur seal *Callorhinus ursinus*, present an interesting case study. Lyamin et al. (2017) examined sleep in the fur seal and observed interesting flexibility (cf. Mukhametov et al., 1985). When on land, fur seals exhibit bilateral SWS and alternation between NREM and REM sleep. On moving to water, however, they switch from bilateral SWS to USWS and exhibit no REM sleep, often for weeks (Lyamin et al., 2018). Additionally, while in USWS, one flipper remains active while the other is inactive. Thus, USWS in the fur seal is different from that in the dolphin. Further, the 'awake' hemisphere does not display all the characteristic neurochemical changes associated with arousal (Lyamin et al., 2017). Elephant seals, in contrast, reduce sleep at sea versus on land, yet seem to spend an equivalent fraction of the sleep in REM sleep (Kendall-Bar et al., 2023).

Monotremes

Monotremes, although mammals, retain some reptilian traits, such as laying eggs. Siegel et al. (1999) examined sleep in the platypus – one of three extant monotreme species. They found rapid eye movements and twitches of the bill and head similar to those seen in REM sleep in therian mammals. However, the EEG signatures in this state show slow waves in NREM sleep, not REM sleep-like activation. Thus, whereas the brainstem displays REM sleep-like features, the forebrain displays NREM features (Siegel et al., 1999).

Reptiles

Recent advances in electrophysiological recordings have allowed for investigations into sleep in lizards. Shein-Idelson et al. (2016) studied sleep in the bearded dragon *Pogona vitticeps* using high-density electrode arrays placed in the dorsal ventricular ridge (DVR). The DVR is a structure in the brains of avians and non-avian reptiles that is thought to be analogous to the mammalian cortex, based on similarities in anatomical organisation and gene expression signatures (Karten, 2015). These recordings revealed two stages of sleep that alternated every 80 s or so. One was characterised by high-amplitude sharp waves (NREM like). The other was characterised by activity similar to wakefulness and more frequent eye movement (REM like) (Shein-Idelson et al., 2016).

Libourel et al. (2018) extended these findings, describing similar states in the bearded dragon and slightly different ones in the Argentine tegu (*Salvator merianae*). Tegu sleep is also characterised by two states – termed S1 and S2. S1 is typified by high-amplitude sharp waves as observed in the bearded dragon. However, the amplitude and frequency of occurrence are lower. S2 is associated with eye movements as in REM sleep, but also with a 15 Hz oscillation in the local field potential not seen in waking – unlike REM sleep. This oscillation is nonetheless susceptible to pharmacological agents that disrupt mammalian REM sleep (Libourel et al., 2018). Despite some differences, at a minimum, both studies describe the existence of two sleep stages in lizards – one REM like and one NREM like.

Larval zebrafish

EEG recordings are impossible in animals without a cortex, such as larval zebrafish (*Danio rerio*). Leung et al. (2019) therefore used whole-brain calcium imaging instead to monitor neural activity

during sleep in restrained larval zebrafish. They monitored heart rate and eye movements concurrent with optical imaging of neural activity. These studies defined two distinct sleep stages in larval zebrafish. These were termed slow-bursting sleep (SBS) and propagating-wave sleep (PWS). SBS is characterised by synchronous activity bursts interrupted by silent periods. SBS is also heightened following sleep deprivation or administration of hypnotics, suggesting that SBS could be a NREM-like state. PWS in contrast, is characterised by a burst of neural activity at onset throughout the neuraxis, followed by a suppression of activity for 20 min. Drugs that induce REM sleep in mammals also induce PWS, suggesting that PWS might be a REM sleep-like state. However, no rapid eye movements were seen during PWS, unlike what might be expected with REM sleep (Leung et al., 2019).

Cephalopods

Careful behavioural and skin-tone observations have been used to define two distinct sleep states in the octopus (*Octopus insularis*) – quiet sleep and active sleep (Medeiros et al., 2021). Animals in quiet sleep are characterised by pale skin and closed pupils. In contrast, when in active sleep, the animals exhibit dramatic changes in skin colour and rapid eye movements. Arousal thresholds were elevated in both sleep states, with the highest arousal thresholds observed in active sleep (Medeiros et al., 2021). A recent preprint extended these findings to describe abnormal sleep behaviours in one octopus (Ramos et al., 2023 preprint). These brief episodes (lasting 44–759 s) occurred during the transitions between sleep and activity states. They consisted of sudden interruptions of sleep through rapid involuntary movements of the arms and body and concomitant colour changes. The octopus then showed typical anti-predator defence behaviours, such as inking using its posterior jet and expelling water from its siphon, suggesting that it may have been acting out a dream (Ramos et al., 2023 preprint). Although these observations were from a single animal, they are interesting and support the idea of active sleep in the octopus being akin to REM sleep.

Similarly, in cuttlefish (*Sepia officinalis*), behavioural observations indicate the presence of two cycling states (Frank et al., 2012; Iglesias et al., 2019). One is characterised by behavioural quiescence, where the cuttlefish rests at the bottom of the tank, often completely covering itself in gravel. The other is typified by quiescence coupled with eye movements and changes in body colouration (Frank et al., 2012; Iglesias et al., 2019). Although no neural activity measurements have been made during these different sleep states in either octopus or cuttlefish, these active sleep states in cephalopods are thought to be REM sleep-like states based on the observation of rapid eye movements. Technologies to record neural activity from octopus brains using implantable electrodes have recently been reported (Gutnick et al., 2023), suggesting that such sleep-specific recordings may be possible in the near future.

Arthropods

Rößler et al. (2021) first noted the existence of a resting state in jumping spiders (*Evarcha arcuata*), during which the spiders would be completely inactive while hanging from a thread in what appeared to be a sleep-like state (Rößler et al., 2021). Inactivity in this position was frequently interrupted by phases of increased activity where spiders showed leg curling behaviours and limb twitching – similar to REM-associated behaviours (Rößler et al., 2021). In more recent work, these observations have been extended to spiderlets, which lack pigmentation, allowing for the visualisation of retinal tubes (Rößler et al., 2022). The authors documented a behavioural state at night characterised by periodic retinal movements, limb twitching and stereotypical leg curling behaviours. Based on these observations, they suggest this state could be a REM sleep-like state. No measurements of arousal thresholds or neural activity were performed, however (Rößler et al., 2022).

In *Drosophila*, sleep has classically been viewed as a unitary state with 5 min of inactivity being used as the threshold to define sleep (Shaw et al., 2000; Hendricks et al., 2000). More recent work indicates a more nuanced picture: sensitive measurements of arousal thresholds and local field potentials (LFPs) suggest the existence of different sleep stages characterised by changes in arousability and LFP power (van Alphen et al., 2013). Tainton-Heap et al. (2021) recently built on this work using volumetric two-photon calcium imaging to define an active sleep state. This state was characterised by waking-like neural activity, short bouts of inactivity (1–5 min), elevated arousal thresholds and decreased responsiveness to visual stimuli. The active sleep state preceded a deep sleep state characterised by lowered neural activity. Potential eye movements, however, were not examined (Tainton-Heap et al., 2021). Indeed, *Drosophila*, possessing compound eyes, have been long thought to be incapable of moving their eyes or retinas and consequently have to perform body saccades to shift their gaze (Cellini and Mongeau, 2020). However, Fenk and collleagues (2022) have recently shown that *Drosophila* can use retinal muscles to perform small saccades that aid in visual motion processing. In the light of these recent developments, it will certainly be of interest to determine whether the active sleep state described by Tainton-Heap et al. (2021) is accompanied by eye movements. In this regard, it is also worth noting the findings of van Alphen et al. (2021), who reported a deep-sleep state in *Drosophila* characterised by proboscis extensions. The existence of multiple sleep stages in *Drosophila* is an exciting finding that has the potential to provide new insights into the evolution and functions of different stages of sleep.

Sleep functions

Sleep supports many functions for the brain and body. Here, we highlight three functions where recent insights have been gained from different taxa – memory, clearance and development – and note parallels with mammalian studies. We note that sleep has also been shown to support immune function and to be modulated in response to sickness in a range of animals (Goetting et al., 2018; Williams et al., 2007; Imeri and Opp, 2009). Unfortunately, because of space constraints, we are unable to discuss this in depth.

Memory

In humans, sleep is required pre-training for the ability to encode new memories and post-training for the consolidation of memory (Drummond et al., 2000; Yoo et al., 2007; Klinzing et al., 2019). The idea that sleep supports neural plasticity, learning and memory is now widely accepted. However, this notion only took flight after the seminal studies of Wilson and McNaughton (1994). In this study, ‘place cells’ in the rat hippocampus were shown to be activated in sequence reflecting the trajectory of the animal along a track (Wilson and McNaughton, 1994). During rest, this sequence was replayed in a time-compressed fashion (Lee and Wilson, 2002; Nadasdy et al., 1999). Further, replay in the hippocampus and cortex appears to be coordinated, and this coordinated replay is critical for the consolidation of the experience into a memory (Siapas and Wilson, 1998; Sirota et al., 2003; Ji and Wilson, 2007; Girardeau et al., 2009). Importantly these place-cell sequences could be

experimentally reactivated in sleep by exposure to a cue (e.g. a context odour or auditory cue) during sleep (Rasch et al., 2007; Bendor and Wilson, 2012).

At first glance, these phenomena, although certainly very interesting, might seem to be restricted to animals with a hippocampus and a cortex. Work in the last few years in honeybees and *Drosophila*, however, suggests that these replay–reactivation phenomena might be more widespread. Zwaka et al. (2015) used classical conditioning of the proboscis extension reflex and a context odour to study sleep-dependent memory reactivation in honeybees. Bees were trained to associate a thermal stimulus with a sugar reward in the presence of a context odour. This context odour was then again presented to bees in deep sleep (as defined by the antennal position). Re-exposure to the context odour during sleep improved recall the next day, suggesting that the cue (in this case, context odour) was reactivating the memory during sleep (Zwaka et al., 2015).

In *Drosophila*, as in humans, sleep prior to training is required for encoding new memories, and sleep post-training supports memory consolidation (Dissel et al., 2015b; Brodt et al., 2023). Further, sleep supports many kinds of memories that use different sensory modalities, including phototaxis suppression, heat box learning, gustatory memory, olfactory conditioning, courtship conditioning and spatial learning (Seugnet et al., 2008; Seidner et al., 2015; Li et al., 2009; Ganguly-Fitzgerald et al., 2006; Melnattur et al., 2021). Dag and colleagues (2019) studied the phenomenon of sleep-dependent memory consolidation using the courtship conditioning paradigm wherein male flies show learned suppression of courtship following repeated rejections by mated females. They found that training activated a specific class of dopaminergic neurons that were then reactivated in sleep. These findings open the possibility that replay-like phenomena might exist in *Drosophila* too.

Sleep is thus clearly important for learning and memory in insects. Recent studies in molluscs and nematodes suggest that sleep's role in supporting learning and memory could extend to those orders as well. In *Aplysia*, the sleep dependence of learning and memory was studied using the 'learning that food is inedible' paradigm, where the animal associates a specific seaweed with failed swallowing attempts. Acute sleep deprivation prior to training impaired learning the next day, whereas sleep loss after training impaired consolidation of the memory into a long-term memory (Krishnan et al., 2016a). Chronic sleep deprivation prior to training also impaired memory, with differential impacts on short- versus long-term memory (Krishnan et al., 2016b).

Further, Chandra et al. (2023) recently described a role for sleep in memory consolidation in the nematode worm *C. elegans* in a surprising and exciting study. The authors used a conditioning paradigm where the worms learnt to suppress their innate attraction to an odour (butanone) by pairing the odour with food withdrawal. Training was shown to increase sleep duration immediately following training. Sleep deprivation in this period impaired memory consolidation. Memory in this task required a pair of interneurons, namely the AIYs, which are one synapse downstream of the AWC chemosensory neurons. Further, using a synapse-targeted GFP reconstitution across synaptic partners (GRASP) technique, the authors showed a sleep-dependent decrease in GFP punctae (and thus presumably synapses) between the AWC sensory neuron and the AIY interneuron (Chandra et al., 2023).

Aplysia have long been a very effective model system to study learning and memory, and *C. elegans* have a simple nervous system with 302 neurons and well mapped out connections. Thus, the results discussed above open the possibility of new mechanistic insights into sleep-dependent memory acquisition and consolidation coming from these models.

Clearance

In the mammalian sleep field, there has been much excitement over the last decade around the discovery of a novel anatomical system for fluid flow in the brain, termed the glial–lymphatic or glymphatic system (Nedergaard and Goldman, 2020). In contrast to many organs and tissues, brain neuropils lack a lymphatic system for fluid flow. Astrocytic processes that express a specific water channel, Aquaporin 4, instead create a conduit for cerebrospinal fluid (CSF) flow across the brain (Iliff et al., 2012; Xie et al., 2013). Driven by arterial pulsations, CSF enters periarterial spaces, mixes with interstitial fluid (ISF) and flows along glymphatic conduits to exit the brain through conduits such as cranial nerves and perivenous spaces (Iliff et al., 2012; Mestre et al., 2018; Xie et al., 2013). This glymphatic flow clears solutes and toxic metabolites, such as amyloid β. Perivenous spaces could eventually drain into lymphatic vessels in the meninges (Wardlaw et al., 2020; Ma et al., 2017; Aspelund et al., 2015). Further, glymphatic flow increased during sleep, particularly SWS (Xie et al., 2013). These findings were exciting, as they suggested a new function for sleep – the clearance of toxic metabolites. Recent work from Ungurean et al. (2023) extends these findings of clearance during sleep to avian brains and suggests that in birds too, ventricular CSF flow is higher in NREM sleep than in waking and REM sleep.

At first glance, given the anatomical differences between vertebrates and invertebrates (e.g. invertebrates have an open circulatory system and an absence of lymphatic vessels), one might expect the clearance function of sleep to be limited to vertebrates. These assumptions, however, were challenged by recent work from van Alphen et al. (2021) that described a specific sleep stage in *Drosophila* defined by characteristic proboscis extensions; this sleep stage seemed to serve a clearance function. This so-called 'proboscis-extension sleep' is associated with elevated arousal thresholds and lowered LFP power, suggesting a deep sleep-like state. Further, impairing proboscis extensions hinders both clearance of injected dyes and recovery from injury (van Alphen et al., 2021). The anatomical basis for this clearance function in *Drosophila* is still unclear. Regardless, these findings are interesting and suggest that, despite anatomical differences, a role for sleep in brain clearance is clearly not limited to mammals.

Development

In humans, other mammals and some birds (e.g. barn owls), the amount of sleep (particularly REM sleep) is elevated in early life at a time of great plasticity (Roffwarg et al., 1966; Frank et al., 2001; Scriba et al., 2013). Sleep deficits in early life can have long-lasting consequences (Halbower et al., 2006; Shaffery et al., 2006; Seugnet et al., 2011; Kayser et al., 2014). Further, sleep deprivation and sleep fragmentation in adult rodents can impair neurogenesis (Guzmán-Marín et al., 2007, 2003). Recent work in *Drosophila* and hydra suggests that the impact of sleep on neurogenesis and cell proliferation more broadly is widespread.

In *Drosophila*, Szuperak et al. (2018) characterised a sleep state in larvae. Using high-resolution video recordings, they showed that 2nd instar *Drosophila* larvae exhibited periods of immobility that met the criteria of a sleep state. Further, they showed that sleep loss impaired neurogenesis as evidenced by fewer numbers of dividing neural progenitor cells (Szuperak et al., 2018). In addition, Kanaya et al. (2020) recently defined a sleep state in *Hydra* as described above. Sleep deprivation by mechanical agitation or

pharmacological agents impairs cell proliferation throughout the body column in *Hydra* (Kanaya et al., 2020). The sleep dependence of cell proliferation in simple organisms such as *Hydra* suggests that sleep could have had a primitive role in development and cell proliferation.

Conclusions and future directions

From being seen as a largely, if not exclusively, mammalian phenomenon, sleep is now generally accepted as being near universal (Joiner, 2016). Sleep states have been described in a range of different taxa. Further, sleep in many taxa appears to be organised into different stages, and sleep functions once thought to be exclusive to 'complex' brains have been observed in animals with small brains. A comparative analysis of sleep across taxa reveals great diversity in sleep behaviour. It is our view that this diversity is not a bug or a glitch in the system, but really the way the system evolved, i.e. that sleep evolved to be plastic. Understanding the plasticity of sleep is thus a crucial if neglected aspect of understanding its control.

There are also many reported functions for sleep. For a long time, sleep researchers have been searching for an elusive elemental molecular or cellular function for sleep which would then explain all sleep-related phenomena. We favour an alternative, more circumspect view; namely, that once a sleep state evolved, different processes were partitioned into this state during evolution, such that there are many functions of sleep. Indeed, a corollary of this view might be that only a portion of the time animals spend in sleep is required for sleep functions. The rest of the time in sleep might perhaps be better ascribed to meeting particular ecological demands or environmental circumstances.

Sleep is seen as a neural phenomenon. However, the precise roles of sleep in neural function and computation remain unclear. Some of the important ideas about the role of sleep in nervous system functioning (Diekelmann and Born, 2010; Tononi and Cirelli, 2003) have been hard to test experimentally, as technologies have been limiting. However, advances in connectomics (Scheffer et al., 2020; Winding et al., 2023) – the ability to record the activity of large ensembles of neurons (Demas et al., 2021) – and the development of simple models of sleep hold the promise of being able to test directly some of these theories.

Although beyond the scope of this Review, an interesting recent study simulated sleep-like phenomena in an artificial neural network to understand sleep's role in neural computation (Golden et al., 2022). Sleep-like replay in this feedforward network was shown to prevent the phenomenon of 'catastrophic forgetting', whereby training the network on a new task overwrites synaptic weights associated with a previous task. Preventing this process of catastrophic forgetting allowed the network to learn multiple tasks sequentially. Sleep was seen to adjust the distribution of synaptic weights to the intersection of the manifolds of the two tasks (Golden et al., 2022). Going forward, more biologically inspired neural networks might allow for better testing of specific hypotheses of sleep function. Indeed, historically, the cross-talk between computer science and biology has greatly advanced neuroscience (Marr, 1982).

Animals without brains proper, such as the cnidarians – jellyfish and hydra – are now generally accepted to sleep. Could animals without neurons sleep? What might such sleep look like? A number of laboratories are actively exploring this question in models such as sponges and placazoans (Pennisi, 2021). Indeed, some hold that sleep is simply a default state (Hinard et al., 2012), and we should really be asking what the function of wakefulness is. As we have covered in this Review, the last 20+ years have seen a flowering of reports of sleep in non-mammalian and invertebrate species that have greatly expanded our understanding of the nature and functions of sleep. The discovery of sleep states in neuron-less creatures has the potential to similarly impact the field and herald a new frontier of sleep studies for the next 20 years.

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Competing interests

The authors declare no competing or financial interests.

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