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Sleep function: an evolutionary perspective

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Abstract

Prospective epidemiological studies in industrial societies indicate that 7 h of sleep per night in people aged 18 years or older is optimum, with higher and lower amounts of sleep predicting a shorter lifespan. Humans living a hunter-gatherer lifestyle (eg, tribal groups) sleep for 6–8 h per night, with the longest sleep durations in winter. The prevalence of insomnia in hunter-gatherer populations is low (around 2%) compared with the prevalence of insomnia in industrial societies (around 10–30%). Sleep deprivation studies, which are done to gain insights into sleep function, are often confounded by the effects of stress. Consideration of the duration of spontaneous daily sleep across species of mammals, which ranges from 2 h to 20 h, can provide important insights into sleep function without the stress of deprivation. Sleep duration is not related to brain size or cognitive ability. Rather, sleep duration across species is associated with their ecological niche and feeding requirements, indicating a role for wake–sleep balance in food acquisition and energy conservation. Brain temperature drops from waking levels during non-rapid eye movement (non-REM) sleep and rises during REM sleep. Average daily REM sleep time of homeotherm orders is negatively correlated with average body and brain temperature, with the largest amount of REM sleep in egg laying (monotreme) mammals, moderate amounts in pouched (marsupial) mammals, lower amounts in placental mammals, and the lowest amounts in birds. REM sleep might, therefore, have a key role in the regulation of temperature and metabolism of the brain during sleep and in the facilitation of alert awakening.

Introduction

Under natural conditions, most diurnal non-human primates go to sleep near sunset and awaken around dawn, sleeping for about 10–12 h.[1] Human beings might be expected to show this same pattern of dusk-to-dawn sleep. However, a 2015 study of hunter-gatherer groups living in a traditional manner in natural environments in Africa and South America has refuted this assumption.[2] This study showed that these populations do not sleep for 10–12 h as do non-human primates; rather, these people sleep for roughly 6–8 h. Another expectation about human sleep is that the artificial environments and electric lighting to

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Declaration of interests

I declare no competing interests.

which industrial populations (ie, people living in societies driven by technology) are exposed might greatly reduce sleep duration by delaying sleep onset. Although insomnia is much more prevalent in industrial populations than in humans living a hunter-gatherer lifestyle,[2] the common assumption that sleep duration in industrial societies has declined over the past 50 years or more has been contradicted by the findings of a literature review of studies of sleep duration in healthy adults.[3]

Sleep duration in humans varies by age, with the longest periods in newborn babies (12–15 h), an intermediate duration in teenagers (9–10 h), and a lower amount of sleep in adulthood (6–8 h). Healthy older people generally maintain this duration of sleep.[4] Racial, ethnic, and sex differences in sleep duration have been noted in studies, but the causes of these variations remain to be determined.[5]

In human adults, both short and long durations of sleep (ie, shorter or longer than 7 h) are associated with poorer health outcomes than a 7 h duration. Epidemiological studies in industrial societies, including as many as 1 million participants who were followed up for a maximum of 6 years, have consistently shown that 7 h of sleep predicts the longest lifespan.[6–10] Pre-existing conditions such as sleep apnoea (which disrupts sleep and extends sleep duration), were controlled for in these studies. A striking finding was that, on average, lifespan was reduced in people sleeping more than 7 h compared with those sleeping less than 7 h.[6–11] No evidence has suggested that sleep restriction in people sleeping longer than 7 h is beneficial. More sleep is not correlated with better health perhaps because sleep is incompatible with activity and exercise, which are well known to promote health.[12] A study of brain grey matter volume, white matter microstructure, and cognitive changes over 28 years in 613 participants of the Whitehall II cohort study found no correlation of these factors with sleep duration.[13] Studies of the duration of spontaneous daily sleep across species of mammal, which can vary from 2 h to 20 h, can provide important insights into sleep function.

In this Review, I discuss the associations between sleep duration, health, and cognition in relation to modern industrial environments. Moreover, I present hypotheses on the function of rapid eye movement (REM) and non-REM sleep across species. This Review is part of a Series of four papers on sleep. The three other papers in the Series are published in *The Lancet* and discuss excessive daytime sleepiness,[14] insomnia,[15] and circadian rhythm disorders.[16]

Effects of the modern environment on sleep

The sleep patterns of humans living a hunter-gatherer lifestyle have been analysed as a means to determine the patterns of human sleep in environments similar to those in which humans evolved—ie, in times before the changes in living conditions brought about by industrial society. Two tribal groups living in Africa (Namibia and Tanzania) and one group living in South America (Bolivia)[2] have been studied. All three of these groups have no electricity, minimal shelters, and are self-sufficient. These groups gather food and have little contact with industrial societies. Activity monitors that do not disturb sleep and have been validated with EEG recording were used to measure sleep duration and timing. All

three groups exhibited similar sleep patterns. Contrary to assumptions that humans living a hunter-gatherer lifestyle sleep from dusk to dawn, individuals in the three tribal groups rarely went to sleep at sunset, with sleep onset occurring (on average) 3·2 h after sunset. The time between sunset and sleep onset was filled with conversation, socialising, and cooking over small fires, with a light intensity (ie, from the fires) generally below levels shown to alter circadian rhythms.[17] These activities are somewhat similar to those occurring in industrialised societies. Indeed, it seems that being awake after sunset is a characteristic that distinguishes human beings from other diurnal primates.[1,2] The studies also showed that, contrary to some speculations about natural human sleep, hunter-gatherers do not regularly awaken in the middle of the night or nap at midday. However, these behaviours do occasionally occur,[2] as they do in industrial societies.

Many species studied in their natural environment have been shown to have pronounced seasonal differences in sleep duration.[18–20] We found that the hunter-gatherer populations sleep for nearly 1 h longer in winter than in summer.[2] Hunter-gatherers sleep during the coldest night-time period, which starts more than 3 h after sunset and ends when the lowest daily temperatures are reached (ie, around dawn). Sleep onset time is much more variable than is sleep offset (ie, awakening) time. This natural situation is in keeping with traditional clinical advice to assist sleep maintenance by lowering night-time temperatures and to awaken at a fixed hour. Hunter-gatherers show peripheral vasoconstriction on awakening in the cold morning,[2] unlike most populations living in industrial societies.

Less than 2% of hunter-gatherers in Namibia and Bolivia reported or showed signs of insomnia, compared with the 10–30% rate of insomnia (depending on the defining criteria) recorded in industrial societies.[21,22] Widespread insomnia is, thus, not a natural characteristic of human beings. The 6–8 h sleep duration of hunter-gatherer groups, which is slightly shorter than the 7–8 h or more duration that has been promoted as a goal in industrial societies,[23] is not incompatible with excellent health. For example, the Tsimane hunter-gatherer group in Bolivia has the lowest rate of coronary artery disease of any studied human population.[24] Hypertension is also rare in hunter-gatherer populations,[25] and prostate enlargement is virtually unknown.[26] Some evidence suggests that Alzheimer’s disease could be relatively uncommon.[27] Obesity and diabetes are also quite rare in hunter-gatherer populations,[28–30] which accords with evidence that food technology in industrial societies has overwhelmed normal human appetite-regulating mechanisms.[31] Hunter-gatherers who move to cities exhibit marked obesity, even exceeding the rates of obesity in industrial societies within a single generation.[32] Because of the low rate of childhood vaccinations in groups living a hunter-gatherer lifestyle, child mortality is high, although vaccination rates have been increasing. For hunter-gatherers who survive childhood, their lifespan is similar to that reported for people living in industrialised societies.[24] The extent to which these features of hunter-gatherer health are dependent on diet, exercise, psychological factors associated with group living, or other variables remains to be determined.

Evolutionary determinants of sleep

Sleep is sometimes said to be a maladaptive state because it increases the vulnerability of animals to predation and is incompatible with eating, reproducing, and protecting offspring.

However, the balance between energy acquisition and expenditure is a key determinant of evolutionary fitness and, hence, reproduction. Because energy expenditure is decreased by inactivity, including during hibernation,[33] estivation (ie, extended periods of dormancy during a hot or dry period), and sleep, these states increase evolutionary fitness. For example, some species of hummingbirds show nightly torpor, a state of greatly reduced body temperature that occurs after the animal goes to sleep. Body temperature can drop from 41°C to as low as 4°C during torpor in several species of Andean hummingbirds.[34] Nightly torpor has been interpreted as an energy-saving adaptation.[34] In mammals, body temperature and energy expenditure decrease during sleep,[35,36] and energy acquisition requires waking. Elephants and other large herbivores maximise their reproductive success by achieving a small but reliable energy surplus through eating large quantities of vegetation. This consumption is directly proportional to the time these animals spend being awake.[37] The optimal balance between activity and inactivity varies by season, and depends on the diet and food availability of each species.

Although energy balance and ecological niches appear to be the main drivers of sleep,[35,38–41] several other ideas have been proposed to explain why mammals sleep. One hypothesis from 2013 is that sleep might enable drainage of toxins from the brain.[42] The evidence for this notion is that the brain's so-called glymphatic system functions better when the brain is relatively inactive (eg, during non-REM sleep and anaesthesia) than when the brain is active.[42] But non-REM sleep is followed by REM sleep in almost all mammals. REM sleep is a state of very high brain metabolic activity that is similar to waking.[43] Therefore, toxin clearance in non-REM sleep would be undone by the re-creation of toxins in REM sleep. Whether there is a net clearance of toxins across the entire natural sleep period in all species remains to be established. Another hypothesis of sleep function is that so-called excess synapses are removed during non-REM sleep. This process is specific for brain region and age.[44] The use of sleep deprivation in studies aiming to determine the function of sleep (eg, to test the synapse removal hypothesis) complicates their interpretation because stress is induced by the experimenter, which is a confounding factor (panels 1, 2).[45–57] Both synapse removal and toxin drainage might occur during sleep, but neither can yet explain the enormous variation in sleep amount across species. Examples of such variation across species are: the differences in sleep duration between carnivores, omnivores, and herbivores;[38,50] the absence of distinctive qualities of human sleep compared with other mammals, despite our high brain-to bodyweight ratio and unique cognitive abilities;[50] and the large seasonal and migratory changes in sleep duration seen in many species, including humans.[2] These differences can be explained by energy conservation benefits and ecological considerations.

Sleep function in homeotherms

Analysis of the correlates of sleep duration across mammals has been used to facilitate understanding of the functional role of sleep. By contrast with sleep deprivation studies, analysing the correlates of sleep duration is not confounded by experimenter-induced stress. In general, species with longer durations of sleep appear to have deeper sleep (ie, the animal is harder to arouse), which is often characterised by the presence of high voltage non-REM sleep (as shown on an EEG) and elevated arousal thresholds to auditory or tactile stimuli.

Most mammals, including humans, sleep for longer periods and have deeper sleep when they are young than when they are mature, although this is not the case with cetacean mammals (eg, whales and dolphins). Do animals that sleep for a longer period have larger brain-to-bodyweight ratios? Do smaller animals, with higher mass-specific metabolic rates and higher rates of free-radical generation, have longer sleep durations than animals with lower mass-specific metabolic rates? Does the lifespan, litter size, or body temperature across species correlate with non-REM or REM sleep duration? These research questions have been studied across species.

No substantial correlation between brain size or brain-to-bodyweight ratio and sleep duration has been reported across species. An inverse correlation between body mass and daily sleep duration was reported in early studies of sleep phylogeny.[58] This finding is a result of large herbivore species (eg, elephants, giraffes, and cattle) having very low amounts of sleep compared with omnivores and carnivores, which is consistent with large herbivores having evolved to spend most of their time awake and eating low-calorie food. However, sleep in carnivores and omnivores does not show a correlation with body mass (figure 1).[38] Across species, in studies done under laboratory or zoo conditions where food is freely supplied (ie, ad-lib), carnivores sleep more than omnivores, and omnivores sleep more than herbivores. Humans, if categorised as carnivores, have the lowest sleep amount of any studied carnivore and, if categorised as omnivores, have the second lowest sleep duration of omnivores (only the common genet [*Viverra genetta*], a type of cat, has less sleep). However, if categorised as herbivores, humans are almost exactly on the line of inverse correlation between body mass and sleep duration, suggesting that reliance on plant consumption had an important role in the evolution of human sleep duration. No evidence is available to show that the herbivore versus carnivore diet itself has a major effect on sleep amount (ie, there is no evidence that human vegetarians sleep for a shorter duration than do human carnivores or omnivores).

Contrary to the idea that sleep amounts are fixed, sleep duration can vary within species because of factors such as environmental temperature, migration periods, and mating behaviour. For example, reindeer (*Rangifer tarandus*) living in the arctic are active for 43% more of the 24 h period in summer (when food is available) than in winter (when snow and ice cover most of the edible vegetation).[59] Migrating animals, such as the white-crowned sparrow (*Zonotrichia leucophrys*), show a profound suppression of sleep during migratory periods. Even when some migrating birds are caged in captivity, sleep is greatly reduced and activity is increased during seasons when they would be migrating in the wild, a phenomenon known as *zugunruhe* in German. This reduction in sleep is not associated with any decrement in learning ability, nor is it followed by a sleep rebound (ie, increased sleep after the end of the migratory period to make up for lost sleep during the migratory period).[19]

African bush elephants (*Loxodonta africana*) in the wild average only 2·1 h of sleep per day, which is the shortest amount of sleep reported in any mammal, and spend nearly all their waking hours eating or walking to find suitable vegetation.[60] The sleep duration of wild African elephants is half the time reported for elephants in captivity, who are fed daily and have an average 4–5 h sleep.[38] Elephants have the largest brain of any land mammal.

Elephants also have a complex social structure, a cognitive ability rivalling that of primates, and one of the longest mammalian lifespans,[37] which is considerably longer for elephants in the wild than for those in captivity.[61]

The animal with the longest documented sleep time is the little brown bat (*Myotis lucifugus*). This animal sleeps, on average, 20 h per day.[39,62] The little brown bat consumes moths and mosquitos; these insects are in their nests during much of the daytime, become active at dusk, and return to their nests as the night progresses and environmental temperature drops. If the little brown bat awakened during the daytime, not only would their prey not be as readily available but also they would be subject to predation by carnivorous birds (eg, hawks and eagles). If the bats stayed out later at night, less food would be available and the cool evening would require greater energy expenditure. Thus, 20 h of daily sleep for the little brown bat is probably not a consequence of needing increased sleep for cognitive processing, but rather a consequence of these bats adapting to their ecological niche, in which their prey is available for a short daily period and their sleeping sites on cave walls or trees are relatively safe.

The functions of REM sleep

REM sleep was discovered in humans by Aserinsky and Kleitman,[63] and first recorded in an animal (the domestic cat [*Felis catus*]) by Dement.[64] REM sleep is seen in most homeotherm species, which include mammals and birds. Mammals can be divided into three subgroups: monotremes (ie, egg-laying mammals, such as the short-beaked echidna [*Tachyglossus aculeatus*] and the platypus [*Ornithorhynchus anatinus*]); marsupials (ie, mammals with pouches for their young, such as the North American opossum [*Lutreolina crassicaudata*], the thick-tailed opossum [*Lutreolina crassicaudata*], and the phalanger [*Trichosurus vulpecula*]); and placentals (ie, mammals that carry their fetus in a uterus, such as whales [Cetacea], elephants [Elephantidae], and humans; appendix). The first study of sleep in a monotreme, the short-beaked echidna, tentatively concluded that this species does not have REM sleep because the studied animals did not show low voltage, cortical EEG during sleep. This feature is characteristic of REM sleep in adult placental mammals.[65] This tentative conclusion would accord with the idea that REM sleep is a phylogenetically new sleep state. However, a subsequent study of sleep in the short-beaked echidna found that, although the cortex shows high-voltage EEG, resembling that of non-REM sleep, the brainstem reticular formation shows burst–pause patterns of neuronal activity, closely resembling the pattern seen in REM sleep, throughout the echidna's sleep period.[66] In a subsequent study, sleep was recorded in another monotreme, the platypus (*Ornithorhynchus anatinus*).[67] REM sleep was observed in the platypus throughout much of the sleep period, although it often occurred during periods in which cortical EEG resembled the high-voltage patterns of non-REM sleep in placental and marsupial mammals, and in birds. This EEG pattern is similar to that recorded in the short-beaked echidna and to that of many newborn placental mammals (including humans). High-voltage cortical EEG is seen during so-called active sleep, which is the developmental precursor to REM sleep. The platypus has more REM sleep than any other animal, and the eye movements are typically accompanied by vigorous jaw and head twitching (video), which are similar to movements that occur in placental mammals during REM sleep. The studies in the short-beaked echidna and

platypus concluded that, contrary to the initial hypothesis, the REM sleep state might be the phylogenetically oldest sleep state in mammals. Monotremes belong to the ancestral line that gave rise to placentals and marsupials.

Three important points should be taken into consideration for understanding the function of REM sleep.[50] First, humans do not have unusually high or low amounts of REM sleep compared with other mammals (figure 2). Second, no obvious relation has been noted between REM sleep duration and presumed cognitive function. For example, the guinea pig (*Cavia porcellus*) has the same sleep parameters as does the guinea baboon (*Papio papio*) and the platypus and little brown bat are not known to have exceptional cognitive capabilities compared with humans and baboons. Third, the amount of REM sleep correlates with the amount of non-REM sleep across mammals (figure 3).

Brain temperature during non-REM sleep is lower than that during waking, but during REM sleep it rises to the brain temperature of waking.[68] During REM sleep, brainstem neuronal activity is greatly increased.[43] Monotremes are thought to have been transitional species between their ectothermic (ie, relying on the external environment to regulate body temperature) reptilian ancestors and endothermic (ie, generating heat to maintain a relatively fixed body temperature) mammals. The warming of the brain that occurs during REM sleep could explain the very long duration of REM sleep in monotremes (figure 4), which have lower body and brain temperatures than other mammals. Monotremes have a brain and body temperature of 31°C, whereas placental mammals have brain and body temperature of 37°C. Allowing brain temperature to fall lower than 31°C while asleep might interfere with autonomic function during sleep and with alert awakening, which is a characteristic of homeotherms that their ectothermic reptile ancestors do not have.[38,69] The marsupial mammals that have been studied (eg, the common bushtail opossum [*Trichosrus vulpecula*], the North American opossum [*Didelphis virginiana*], and the big lutrine opossum [*Lutreolina crassicaudata*]) have a body temperature higher than that of monotremes but lower than that of placentals. The daily REM sleep duration for marsupials (about 4·4 h per day) is lower than that for monotremes (about 7·5 h per day), but higher than that for placentals (about 2·0 h per day). The placental mammal order has higher body temperatures and lower average daily REM sleep duration than marsupials. Within the group of placental mammals, body temperatures are relatively fixed across species, and the ecological variables described in figure 1 are correlated with sleep duration. Birds have the highest body and brain temperatures of all homeotherm species (core temperature of 41°C), as well as the highest metabolic rates[70,71] and the lowest daily amount of REM sleep (about 0·7 h per day—ie, a tenth of the amount of REM sleep in monotremes). Body and brain (including brainstem) temperature is a major (inverse) correlate of REM sleep time across homeotherm orders (figure 4).[69–73]

REM sleep might have initially evolved to maintain brainstem function during sleep in mammals that had relatively low body temperatures and metabolic rates, which is a characteristic of the monotreme mammals. REM sleep might be thought of as a thermostatically controlled brain-heating mechanism, which is triggered by the temperature reduction linked to the reduced metabolism and the decrease in energy consumption in

non-REM sleep.[74,75] Then, REM sleep ends after the amount of REM required to raise brain temperature to close to the waking temperature of the body has occurred.

As marsupials and placentals with a higher body temperature and a proportionately larger forebrain have evolved, REM sleep activation has extended to the cortical regions, but its duration has decreased. The decerebrate mammal (ie, with the brainstem experimentally disconnected from the forebrain at the midbrain–forebrain junction) cannot thermoregulate. The body temperature of the decerebrate mammal, including the temperature of its blood, drifts towards room temperature if no external heat is applied (eg, through a heating pad). The pontine region of the brain is both necessary and sufficient for the generation of REM sleep, as revealed by systematic studies in domestic cats.[76–78] Removing external heat from a decerebrate animal and allowing body temperature to fall to 23°C (ie, to room temperature) increases REM sleep duration, with REM sleep reaching 70% of the recording time (figure 5)[79] and REM sleep periods lasting for as long as 45 min.[80] This finding illustrates the thermosensitivity of the brainstem mechanisms generating REM sleep, with REM sleep being triggered by low brainstem temperatures, and increasing the temperature of the brain. By contrast, intact cats (ie, domestic cats that have not had their brainstem disconnected) have, on average, REM sleep for 15·5% of total sleep duration at thermoneutral temperatures,[81] which is commensurate with the fact that intact cats have a smaller reduction in brain temperature during non-REM sleep than decerebrate cats. The intact cat never shows the long duration of REM sleep periods seen in the cold decerebrate cat.

These data together suggest that REM sleep has a thermoregulatory role for the brain, which is triggered by decreases in brainstem temperature during non-REM sleep, and ceases when the target temperature is reached, in a repeating cycle. Because the decerebrate animal cannot regulate its body temperature, the body and brain temperatures (including brainstem temperature) fall precipitously when external heating is removed, despite REM sleep activation. Therefore, REM sleep occurs nearly continuously. It could be said that REM sleep is like shivering for the brain.[82]

In intact mammals (ie, mammals without a brain lesion or disconnection), REM sleep is normally triggered after non-REM sleep, which prevents brain temperature from falling far below the temperature required for alert waking on arousal. This occurrence fits with the known increase in REM sleep toward the end of the human sleep cycle,[4] at a time when environmental and body temperature is generally low[2] and waking is imminent. The reduced body temperature during non-REM sleep provides a major energy benefit, because a large percentage of our energy consumption at rest is used to maintain body and brain temperature.[35] REM sleep periods typically follow non-REM sleep periods, consistent with a cycle of brain cooling during non-REM sleep followed by brain warming and correlated increases in brain metabolic rate,[68,83,84] which are optimal conditions for alert awakening.

Body thermoregulation is maintained during non-REM sleep, albeit at a lower temperature than during waking. In REM sleep, brain temperature is increased from the temperature that occurs during non-REM sleep but body muscle tone and thermoregulation are greatly diminished. Body temperature will either increase or decrease depending on environmental

temperature.[84] This combination of thermoregulatory changes that occur during REM sleep serves three functions. First, heating the brain keeps it metabolically functional and able to rapidly awaken. Second, reducing or eliminating activity in the muscles of the body saves energy. Third, reducing muscle tone prevents dream-enacting behaviours that are generated by pontine activation in REM sleep.[85] When the muscle tone suppression mechanism of REM sleep is damaged, REM sleep behaviour disorder occurs (panel 3).[86–94]

REM sleep can be pharmacologically suppressed in humans for weeks to months by monoamine oxidase inhibitors such as phenelzine.[95] No periods of rapid eye movement occur, no periods of REM sleep-like EEG activation occur, and no dreams are reported.[95] This suppression is not accompanied by any detected disturbance of cognitive function. The reduction of REM sleep by serotonin and norepinephrine reuptake inhibitors also has no negative effects on memory.[96] No relation has been noted between measures of human intelligence and REM sleep duration.[97] Moreover, in a rare case, an individual who survived damage to the pontine region, which is known to generate REM sleep, showed average or above average learning and cognition on various tests despite minimal amounts of REM sleep.[98]

Non-REM sleep and REM sleep in marine mammals

The adaptations that have evolved in marine mammals provide important insights into the functional roles of mammalian sleep states. Extant marine mammals have very large brains and high brain-to-bodyweight ratios, which are almost as high as the brain-to-bodyweight ratios seen in primates.[99,100] Common bottlenose dolphins (*Tursiops truncatus*) have brains that are substantially larger than human brains. However, instead of the bilateral slow waves seen during sleep in land mammals, these dolphins only have unihemispheric slow waves during sleep. This type of sleep has been described as unihemispheric sleep or half brain sleep. In contrast to all previously studied mammals, no evidence has been found that dolphins have REM sleep (figure 2), with similar findings in other cetacean species.[99]

Because most land mammals have their longest durations of REM sleep shortly after birth, with a reduced duration of REM sleep in adults, the idea was proposed that newborn dolphins might show REM sleep, which would be consistent with the hypothesis that REM sleep plays an essential role in neural development. However, not only do newborn dolphins and killer whales (*Orcinus orca*), which are the largest species of the dolphin family, not show REM sleep, but they do not sleep at all for several weeks after birth.[101] In the wild, killer whale calves and their mothers (and other cetaceans) often migrate for thousands of miles after birth to get from their birthing area to feeding areas. This migration requires high levels of alertness and sensory motor control, because the calves are subject to predation by sharks and other killer whales, which means that the mother and calf must stay together and be responsive to threats.

The absence of REM sleep in dolphins was put into a larger context by work in fur seals (*Callorhinus ursinus*).[102] Fur seals have about 80 min of REM sleep per day and about 5–6 h of non-REM sleep per day when they sleep on land, with bilateral high-voltage cortical activity, similar to the sleep amounts in humans. When fur seals go into water, which is their

home for about 7 months of the year, they do not show the bilateral non-REM sleep that they have when on land. Instead, fur seals show unihemispheric high-voltage activity, similar to that seen in the dolphin and other cetacean species. Fur seals also largely cease having REM sleep when they are in water. Moreover, when fur seals return to land, they do not show the large increase in non-REM and REM sleep that can be seen after sleep deprivation in terrestrial mammals.[102]

Unlike bilateral non-REM sleep, unihemispheric sleep might not cool the brainstem. This absence of cooling could enable cetaceans to maintain coordinated brainstem motor and sensory function, despite unihemispheric cortical slow waves. Because of the absence of cooling, warming of the brainstem with REM sleep would be unnecessary. This hypothesis could be tested in fur seals by comparing their brainstem temperatures during sleep on land with brainstem temperatures during unihemispheric sleep when they are in the water environment.

Non-homeothermic animals (ie, poikilothermic species such as reptiles and insects) vary their activity over the 24 h cycle. Inactive states in these creatures might serve the same energy conservation function as sleep does in homeotherms. However, whether these inactive states are homologous (ie, coming from a common evolutionary root) or analogous (ie, serving a similar function by using an unrelated biological mechanism) is unclear (panel 4).[103–108]

Conclusions and future directions

Sleep is a highly adaptive brain function because it reduces energy expenditure. Insomnia is common in humans living in industrial societies, which is probably due, at least to some extent, to the removal of natural temperature and light cycles from the modern environment. The means by which environmental variables affect neurons regulating sleep remain to be determined. Body and pontine brainstem temperature recordings should be done during animal sleep recordings to better understand the relation of sleep to thermoregulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel 1:

Limitations of studies using sleep deprivation

A traditional approach to determining the function of sleep is to deprive animals of sleep and attribute any resulting deficits to the loss of sleep function. This approach is problematic because of the stress involved in sleep deprivation. Deprivation typically involves repeated arousal of the studied animal as the animal drifts into sleep. Such arousals generate the cortisol awakening response.[45,46] Awakening is associated with rapid (burst) firing of neurons in most brain regions.[43] The disk-over-water technique (developed for sleep deprivation studies in rats), although appearing gentle, results in over 1000 awakenings per day.[47–49] Although rats die after 2 or more weeks of this procedure,[52] the neuronal and systematic stress resulting from such awakenings cannot be separated from the loss of sleep time. Similarly, sleep deprivation by gentle handling, often used in sleep deprivation studies in mice, requires repeated arousals as animals drift into sleep. Experimental sleep deprivation in humans might qualitatively differ from animal sleep deprivation studies because the human participant volunteers for the procedure. Nevertheless, arousals from the sleepy state or from brief sleep onsets interrupted by the experimenter can be expected to repeatedly generate the physiological awakening response, which might, by itself, cause the induced symptoms.

Panel 2:

Sleep and memory consolidation

An important variable in experimental studies on sleep and memory consolidation that has not been adequately controlled for is interference. Sleep deprivation might diminish recall, not by preventing memory consolidation but rather by increasing waking and its accompanying learning, which competes for consolidation with the learning measured by the experimenter,[54–56] and by inducing stress. Relaxed quiet waking can be as effective as sleep in promoting recall of items presented by the experimenter.[50–56] A study of the relation between REM sleep, non-REM sleep, other sleep parameters, and memory consolidation in more than 900 participants did not find any correlation between the sleep parameters and memory consolidation.[57] Another study with over 900 participants on intra-individual differences in sleep parameters and recall also found no correlation between the memory consolidation and sleep parameters.[53,54]

REM=rapid eye movement.

Panel 3:

REM and non-REM sleep pathologies

- Muscle tone is moderately reduced in non-REM sleep but is actively suppressed during REM sleep; this suppression is accomplished via inhibition by GABA and glycine release onto motor neurons, along with disfacilitation by reduction in monoamine release onto these neurons;[85–87] this reduction in skeletal motor activity prevents the sleep disruption that would result from the very high level of activity of pontine brainstem movement-related neurons in REM sleep[47,85–87]
- Bilateral damage to the brainstem motor suppression systems, particularly to regions that are just ventral to the locus coeruleus,[85] results in REM sleep without atonia, in which extensive motor activity occurs during REM sleep; REM sleep behaviour disorder can occur in humans and causes apparent dream-enacting behaviours; in contrast to the localised lesion in this animal model, REM sleep behaviour disorder is a synucleinopathy, with no discretely localised lesion; more than 80% of individuals with REM sleep behaviour disorder go on to develop Parkinson's disease[87,88]
- In obese individuals with narrowed airways, and in some individuals with small airways and normal weight, the suppression of pharyngeal muscle tone in REM sleep can cause an occlusion of the airway. Occlusion of the airway can result in sleep apnoea, cyclically alternating with arousals, leading to sleep fragmentation, oxyhaemoglobin desaturation, hypertension, cardiovascular disease, and other related problems; sleep apnoea can be successfully treated with continuous positive airway pressure applied through a facial mask or directly through the nose[89]
- The pathology underlying the common syndrome of periodic movements during sleep in individuals with restless legs syndrome remains to be elucidated, although iron deficiency and dopamine appear to have central roles[90]
- Narcolepsy is caused by a loss of hypocretin neurons[91,94] and can be associated with psychological depression and loss of muscle tone with emotions in waking (cataplexy);[92,93] this sleep disorder is discussed in more detail in the second paper in *The Lancet* Series on sleep, which is on excessive daily sleepiness[14]

REM=rapid eye movement.

Panel 4:

Inactive states in non-homeothermic species

Some cicada species are successful because they limit activity to a 2–4 week period, then become inactive for as long as 17 years.[103] A similar phenomenon has been reported in millipedes.[104] Small fruit flies (*Drosophila melanogaster*),[105] free-living nematodes (*Caenorhabditis elegans*),[106] and zebrafish (*Danio rerio*)[107] have states that have been described as sleep-like. However, the differences between mammalian brains and the neuronal organisation of these poikilothermic organisms make functional comparisons difficult. In the only study of brainstem neuronal activity during sleep in a reptile,[108] no evidence was found for a REM sleep-like state. It cannot be assumed that all states of reduced behavioural activity are homologous to mammalian sleep states.

Search strategy and selection criteria

I searched MEDLINE and Google with the keywords (“sleep” AND “neurons”), (“sleep” AND “cognition” OR “learning”), “sleep function”, (“sleep” AND “mammals”), and “sleep phylogeny”. The search was restricted to publications from Jan 1, 2000, to June 1, 2021, with no language restrictions. I also included key references from before 2000.

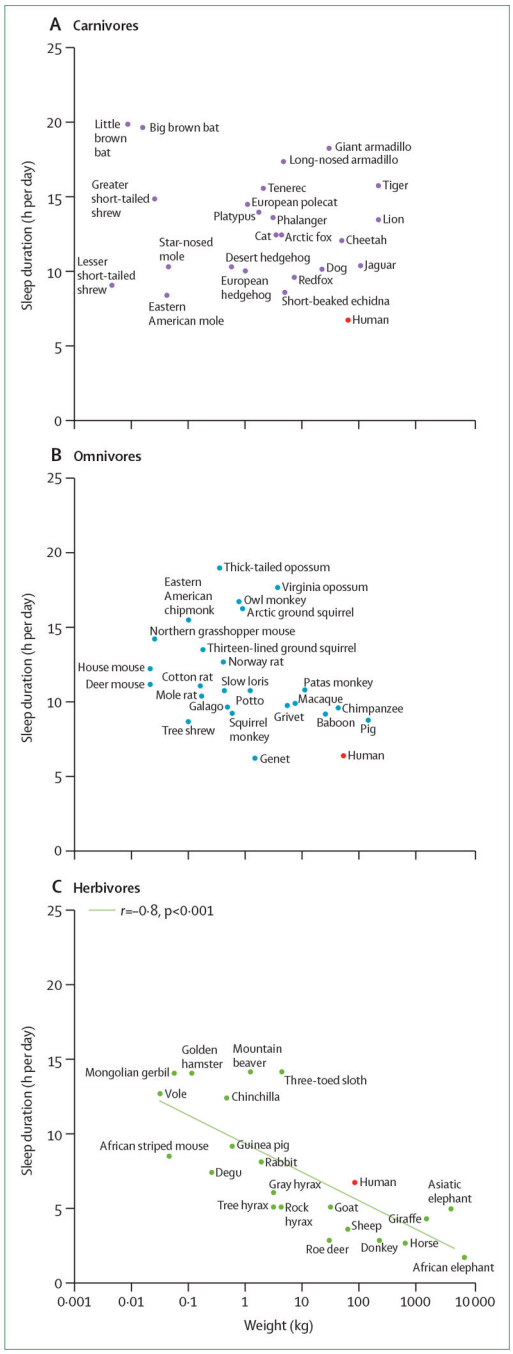

Figure 1: Sleep duration in mammals

Graphs show the sleep duration of carnivores, omnivores, and herbivores. Sleep data are compiled from various studies, many of which were done in zoos or laboratories.[38] The red dot highlights data for humans on each graph. Weight is plotted on a logarithmic scale. Log values for weight were used in correlation calculations versus linear values for sleep duration. The sleep durations of carnivores, omnivores, and herbivores differ significantly ($p<0{\cdot}0002$; *f* test). The sleep durations of carnivores are significantly greater than those of herbivores ($p<0{\cdot}001$; *t* test). Sleep amounts in herbivores are negatively correlated with

weight (r=−0·8; p<0·001). However, the correlation between weight and sleep time is not significant in carnivores (r=−0·3) or omnivores (r=−0·3).

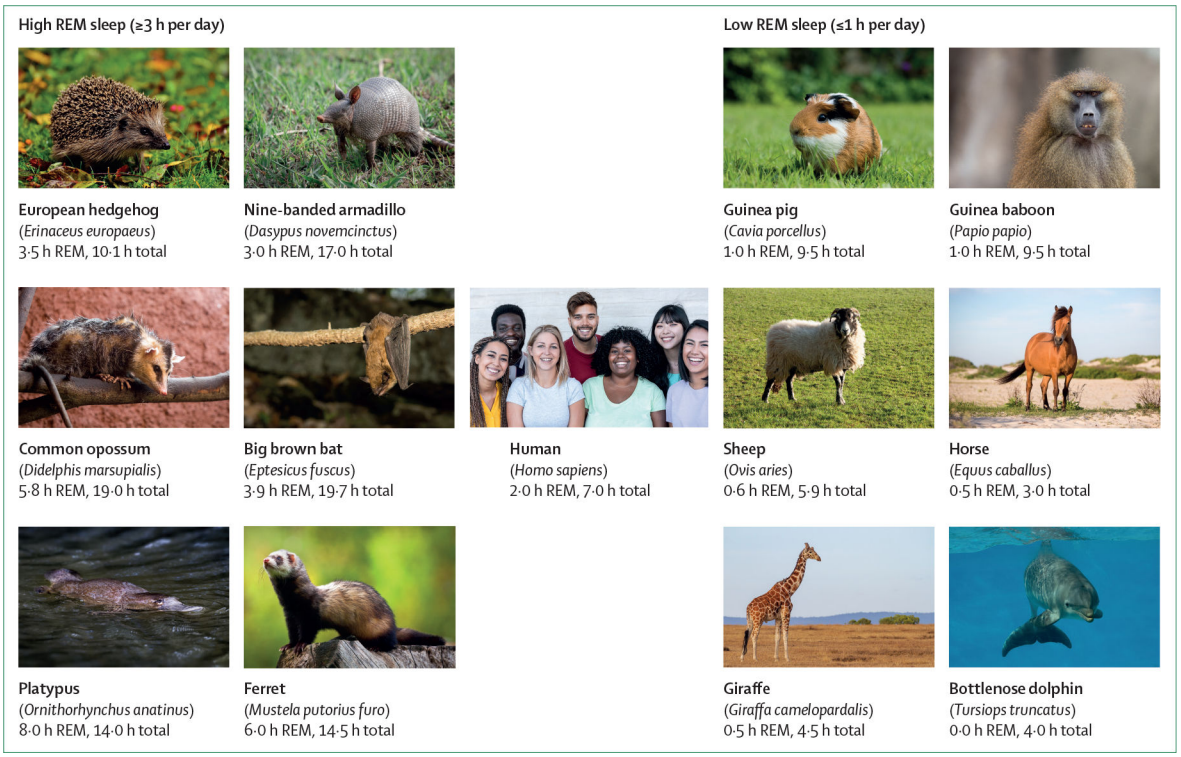

Figure 2: REM sleep duration across species

REM sleep time and total sleep time are shown for a selection of mammalian species. In contrast to other placental mammals, dolphins and other cetaceans only have unihemispheric sleep, so sleep time in dolphins is presented in this figure as half of the total 8 h unihemispheric sleep time. This figure was adapted from reference 50, with permission of the American Association for the Advancement of Science. REM=rapid eye movement. Photo credits: platypus, Martin Pelanek/Shutterstock; opossum, Vladislav T Jirousek/ Shutterstock; ferret, jurra8/Shutterstock; big brown bat, Jay Ondreicka/Shutterstock; hedgehog, Vy nguyen 2905/Shutterstock; armadillo, Marcelo Morena/Shutterstock; humans, DisobeyArt/Shutterstock; guinea pig, Birute Vijeikiene/Shutterstock; guinea baboon, Nagel Photography/Shutterstock; sheep, Dawn Quadling/Shutterstock; horse, Mary Swift/ Shutterstock; giraffe, Nicola_K_photos/Shutterstock; dolphin, Luis Seijido/Shutterstock.

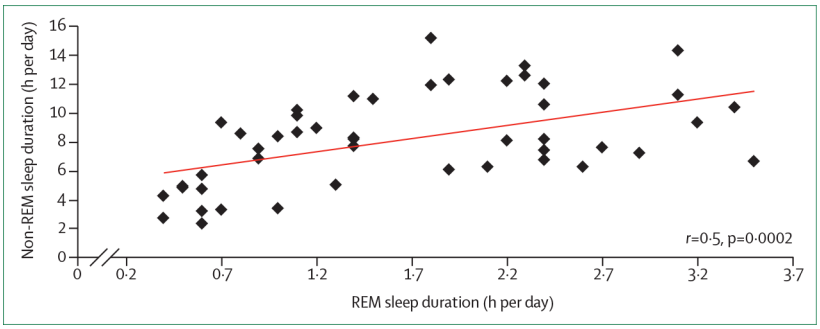

Figure 3: REM versus non-REM sleep duration across placental mammalian species

REM sleep duration is correlated with non-REM sleep duration across 47 placental mammalian species (r=0·5, p=0·0002). REM sleep and non-REM sleep data are shown in the appendix (pp 1–3). REM=rapid eye movement.

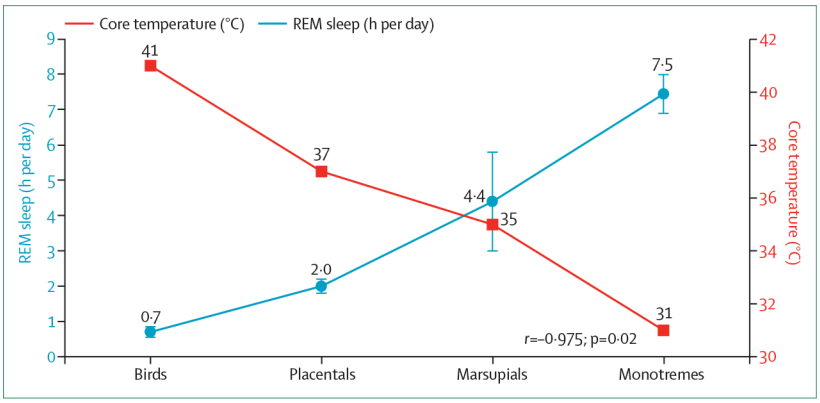

Figure 4: REM sleep hours per day versus core body temperature in homeotherm orders

Homeotherms with the highest body temperature (birds) have the lowest amount of REM sleep, with this inverse relation between temperature and REM sleep duration continuing across placental, marsupial, and monotreme species. Many bird and placental species have been studied, hence the very small standard error for their mean REM values. Overall, there is a negative correlation of core temperature with REM sleep duration across orders (r=−0·975; p=0·02).[69–73] REM sleep data are shown in the appendix (pp 1–3). REM=rapid eye movement.

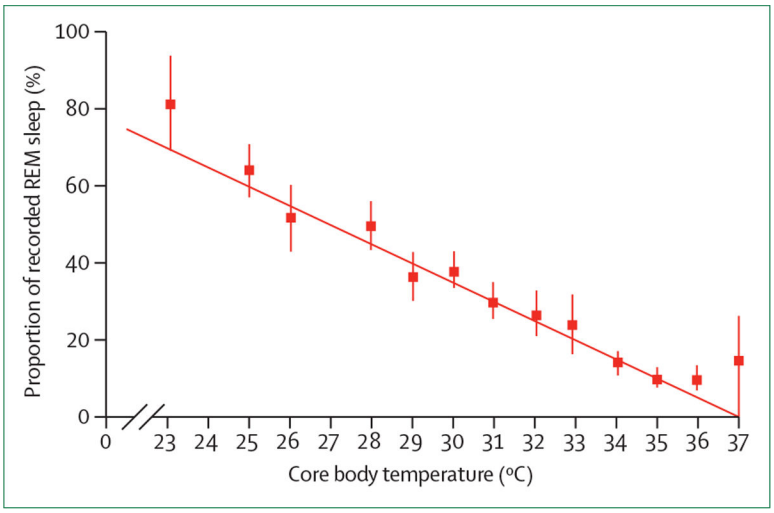

Figure 5: Effect of brain temperature on REM sleep

The decerebrate animal (ie, with the brainstem experimentally disconnected from the forebrain at the midbrain–forebrain junction) cannot regulate body temperature, which then falls towards room temperature. Data from decerebrate domestic cats (*Felis catus*)[78] show the effect of passive cooling of the pontine brainstem region, the region which is both necessary and sufficient for REM sleep, on the proportion of REM sleep. As core temperature falls, REM sleep increases well beyond the highest amount of REM sleep seen in the intact cat. Vertical lines represent standard errors, and the boxes denote the mean value. Graph drawn from data in reference 80. REM=rapid eye movement.