Sleep Medicine Reviews (2007) 11, 405–409

SLEEP MEDICINE reviews

www.elsevier.com/locate/smrv

INVITED COMMENTARY

The non-trivial functions of sleep

Niels C. Rattenborg[a,*], John A. Lesku[a], Dolores Martinez-Gonzalez[a], Steven L. Lima[b]

[a]*Sleep and Flight Group, Max Planck Institute for Ornithology—Seewiesen, Starnberg, Germany*
[b]*Department of Ecology and Organismal Biology, Indiana State University, Terre Haute, USA*

Introduction

In "*The trivial function of sleep*", Rial et al.[1] present a provocative argument against a function for sleep other than simple rest when animals have nothing else to do. Under this hypothesis, the circadian rhythm of poikilotherms is thought to be sufficient to enforce rest at night, whereas true sleep with homeostatic regulation evolved only in homeotherms to ensure periods of inactivity in these "warm-blooded" animals that could conceivably be continuously active day and night. Although we acknowledge that our understanding of the functions of sleep are far from complete, we find the argument that sleep is a "junkyard" of non-adaptation to be unconvincing, especially when considering the dangers inherent in sleep and recent evidence for sleep-dependent memory processing and plasticity.[2–4]

A discussion of all the points put forth by Rial et al. is beyond the scope of our commentary. Consequently, we restrict our comments to a few select topics. A discussion on this group's ideas on the evolution of slow-wave sleep (SWS) in mammals and birds from reptilian wakefulness, briefly mentioned in the article under consideration, has already been published.[5–7] For the sake of comparison and clarity, we will use the same sleep-related terminology as in Rial et al.[1] e.g., *rest* for poikilotherms and *sleep* for homeotherms. Nevertheless, as discussed below, we conclude that the evidence for true sleep in a wide range of poikilotherms is convincing.

Rest (sleep) homeostasis in poikilotherms

Rial et al. propose that sleep homeostasis evolved independently in mammals and birds to enforce a period of inactivity. According to this idea, poikilotherms did not require rest homeostasis, because the circadian rhythm was sufficient to enforce rest at night. However, evidence exists for rest homeostasis in invertebrate[8] and vertebrate[9] poikilotherms. Rial et al. challenge the evidence for rest homeostasis in poikilotherms by noting that increases in rest following rest deprivation may reflect fatigue or stress resulting from the deprivation procedure, rather than an increased need for rest. Although this was perhaps a valid concern in the past, recent studies in insects have effectively addressed this issue. Shaw et al.[10] showed that the increase in rest following rest deprivation in fruit flies (*Drosophila melanogaster*) was not correlated with the amount of activity induced during deprivation. Likewise, stimulating flies during their normal period of wakefulness also had no effect on rest[11] or actually decreased rest during the following night,[10] a pattern unexpected if the rest

*Corresponding author. Max Planck Institute for Ornithology—Seewiesen, Sleep and Flight Group, Postfach 1564, D-82305 Starnberg, Germany.
E-mail address: rattenborg@orn.mpg.de (N.C. Rattenborg).

1087-0792/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.smrv.2007.04.003

rebound following deprivation was due to fatigue. Similar results have also been found in bees (*Apis mellifera*).[12] Consequently, rest in insects seems to be homeostatically regulated.

Rial et al.'s hypothesis also suggests that insects lacking a circadian rhythm should not rest. As in mammals, however, flies lacking a circadian rhythm due to a mutation in the circadian *per*^{01} gene still rest and even show an increase in rest following deprivation.[10] The presence of homeostatically regulated rest in the absence of a functional circadian rhythm challenges the notion that rest is simply enforced by the circadian rhythm, and together suggests that rest serves more than a trivial function.

Rest (sleep) and memory processing in poikilotherms

Recent studies suggest that rest in fruit flies may be involved in memory processing and plasticity.[13–16] For instance, fruit flies exposed to a learning enriched environment early in life spend more time resting later in life than those exposed to a learning impoverished environment.[16] Importantly, the increase in rest following exposure to an enriched environment is dependent upon genes involved in long-term memory. The presence of rest homeostasis and evidence for sleep-dependent memory processing and plasticity in insects pose a significant challenge for Rial et al.'s hypothesis for the trivial function of sleep.

SWS homeostasis and memory processing in homeotherms

Several aspects of sleep in homeotherms are also inconsistent with Rial et al.'s hypothesis. Rial et al. suggest that sleep homeostasis evolved in homeotherms to enforce a period of rest without which such animals could be continuously awake. According to this idea, the transition from being diurnal to nocturnal in early mammals negated the involvement of the circadian system in determining the timing of inactivity. As a result, mammals needed another mechanism to enforce a period of inactivity, because continuous activity would presumably be maladaptive. According to Rial et al., true sleep with homeostatic regulation evolved to fulfill this function. If for the sake of discussion we ignore the evidence above for rest (sleep) homeostasis in insects,[10–12,17] and assume that the function of sleep in homeotherms is to enforce a period of inactivity, it is still unclear why the intensity of SWS should increase following sleep deprivation in mammals[8] and birds.[18] An even greater challenge for Rial et al.'s hypothesis is the fact that SWS is regulated locally in the neocortex in response to prior use during wakefulness in mammals,[19] including humans.[20,21] Why should brain regions preferentially activated during prior wakefulness sleep more intensely if the primary function of sleep is simply to cause the whole animal to remain inactive? More problematic is the finding that the degree to which SWS intensity increases in brain regions utilized during prior learning predicts enhancements in performance the next morning.[20] This and other evidence from mammals,[2,22] birds[23] and insects (see above), clearly indicate that the relationship between sleep and memory processing is far from trivial.

Animals are vulnerable during sleep

Throughout their paper, Rial et al. assert that the function of sleep is to enforce a period of inactivity. It is unclear, however, why a period of unconscious inactivity is necessarily beneficial, particularly one accompanied by the profound vulnerability that defines sleep in poikilothermic and homeothermic animals. Although it has been argued that the reduction in sensory responsiveness that defines sleep is required to prevent animals from expending energy and increasing their conspicuousness to predators by responding inadvertently to irrelevant stimuli[24,25] (see also Lima et al.[26]), most, if not all, animals are better able to detect predators and decide whether fleeing or freezing is the safest option when awake than when asleep. Consequently, the fact that all animals studied sleep strongly suggests that sleep must serve an essential function with benefits that outweigh the potential cost of predation.

Our work on sleep and predation in birds demonstrates the inherent conflict between the simultaneous need to sleep and watch for predators. In addition to sleeping with both eyes closed, birds are able to sleep with one eye open, a behavioral state associated with a SWS electroencephalogram (EEG) pattern in the hemisphere opposite the closed eye and EEG activity intermediate between SWS and wakefulness in the hemisphere opposite the open eye.[27] Birds can switch between sleeping with both eyes closed to sleeping with one eye open in response to a perceived increase in the risk of predation. Mallard ducks (*Anas platyrhynchos*) sleeping at the edge of a group, a position that birds perceive as dangerous, spend proportionately more time sleeping with

one eye open than those safely flanked by other birds.[28] Moreover, when sleeping with one eye open, mallards at the periphery of a group direct the open eye away from the other birds, as if watching for approaching predators. By sleeping with one eye open, mallards are apparently attempting to mitigate the conflict between the simultaneous need to sleep and remain vigilant for predators. In contrast, according to Rial et al.'s proposal, mallards that perceive a risk of predation should simply stay completely awake, thereby maximizing their ability to detect and respond to a predator. Instead, the compromise between sleep and wakefulness displayed by mallards suggests that they acquire some of the benefits of SWS in the sleeping hemisphere, while still watching for predators with the other hemisphere.

As in birds, the sleep patterns of dolphins and porpoises pose a significant challenge for Rial et al.'s hypothesis that inactivity is the trivial function for sleep. These Cetaceans can swim and surface to breathe while one hemisphere shows EEG activity indicative of SWS and the other shows activity indicative of wakefulness.[27,29] Swimming during such unihemispheric SWS is clearly inconsistent with inactivity as the default function for sleep. Although one might question whether the presence of unilateral high-amplitude, slow waves in the EEG during swimming truly reflects sleep, especially given that immobility is traditionally one of the defining features of sleep, this argument is unsatisfactory because it does not explain the presence of unilateral slow waves. Furthermore, Cetaceans usually close the eye contralateral to the hemisphere with slow waves and thereby reduce their ability to detect approaching predators.[30] The most parsimonious interpretation here is that this unihemispheric phenomenon is a specialized form of SWS that can occur concurrently with activity.

The fact that animals sleep, despite the inherent risk of predation, or need for continuous activity in the case of dolphins and porpoises, indicates that sleep must serve an essential function with benefits that outweigh the potential cost of predation. Moreover, it suggests that the functions of sleep can be achieved only in the absence of significant sensory input. Indeed, sensory processing and certain forms of memory processing[2] and plasticity (e.g., synaptic downscaling) may be incompatible; i.e., "*… sleep is the price we have to pay for plasticity …*".[4] Even if these sleep functions could be carried out locally in the brain while the animal is mostly awake and responsive, there are adaptive reasons for consolidating such functions into a single, largely whole brain (or hemisphere) unconscious period of sleep.[31]

Natural selection acts on sleep

The ubiquity of sleep in the animal kingdom, even under dangerous circumstances, suggests that sleep must serve an essential function favored by natural selection. However, Rial et al. suggest that the opportunity for natural selection to act upon SWS and rapid eye movement (REM) sleep is limited because these states are usually indistinguishable based on behavior. To illustrate their point, Rial et al. suggest that a farmer who wanted to select for animals with high amounts of REM sleep would be hard pressed to choose the right individuals for breeding. This argument for the absence of natural selection on sleep is unfounded, however, because it assumes that natural selection acts only on phenotypes directly visible to a selective force. In animals where SWS and REM sleep are not distinguishable based on behavior alone, natural selection could nonetheless act indirectly on REM sleep through its interrelationship with performance during wakefulness.[2]

Natural selection may also act more directly on sleep. In fact, for large herbivores, REM sleep might have an immediate consequence related to predation. Specifically, many large herbivores can engage in SWS while standing, but must lie down for REM sleep,[32,33] a behavioral state that predators could use to target vulnerable prey. Indeed, a recent comparative analysis of mammalian sleep times found that species exposed to greater risks of predation engage in less REM sleep and allocate a lower proportion of time asleep to REM sleep.[34] Collectively, these relationships suggest that REM sleep is a particularly dangerous sleep state, possibly due to high associated arousal thresholds and muscle atonia, and are consistent with experimental work in mice.[26,35] Thus, the evolutionary preservation of some REM sleep, despite selection from predators against REM sleep, indicates that such sleep must serve an important function.

Rial et al. also propose that REM sleep may be functionless and incorrectly cite a lack of phylogenetic correlation as support for this claim. Several comparative studies of mammalian sleep times have evaluated interspecific support for the function of both SWS and REM sleep (reviewed in Lesku et al.[34]). Some of these studies found that species with greater encephalization, a purported index of cognitive abilities, allocate a lower proportion of time asleep to REM sleep,[36,37] a finding that would seem to challenge a neurophysiological role for REM sleep, such as memory processing and plasticity.[38] However, this negative relationship is actually due to the lack of appropriate phylogenetic control within these analyses. Recently, Lesku et al.[34]

analyzed the mammalian dataset while controlling for shared evolutionary history among species, and found that species with greater encephalization actually allocate *more* time asleep to REM sleep, thereby demonstrating comparative support for a neurophysiological role for REM sleep. Moreover, this positive relationship is consistent with experimental data showing that REM sleep plays a role in memory processing and plasticity in birds[39] and mammals.[2]

Another evolutionary point concerns the fact that the "junk DNA" analogy used by Rial et al. to explain the complexity of sleep, actually argues against their main thesis. Such inconsequential DNA does seem to exist, as it readily mutates without any apparent consequences. As a result, this junk DNA will diverge widely in sequence as time proceeds, such that the (junk) base-pair sequences of distantly related species may vary greatly (this is why such base-pair sequences are valuable in reconstructing phylogenetic trees). If sleep were really an analogous evolutionary junkyard, then one would not expect the characteristics of sleep to be conserved over evolutionary time, since the only thing that would matter is sleep and not the details of sleep itself. It would, in fact, be very likely that the electrophysiological correlates of sleep would vary dramatically as the species being compared become more distantly related to each other. There would certainly be no reason to think that SWS or REM sleep would be conserved entities under the junkyard scenario, or that they would correlate with ecological and constitutional traits, as discussed above.[34] Such correlations and the observation that SWS and REM sleep have been conserved across mammalian evolution[37] suggest an important role for these forms of sleep, not an evolutionary junkyard.

Finally, we should also point-out that Rial et al.'s view of accepting adaptation as a last resort is contrary to current practice in the evolutionarily based study of animal behavior. A much more prevalent, and productive, approach is one in which adaptation is assumed to exist via the power of natural selection; the main task is to erect several competing hypotheses about the nature of that possible adaptation and then to test them against observations. This method is widely used and known generally as the adaptationist approach[40] (see also Stephens and Krebs[41] and Mitchell and Valone[42]). Non-adaptation is an outcome accepted only after all reasonable adaptive hypotheses has been exhausted. The non-adaptationist approach espoused by Rial et al. impedes progress toward a comprehensive understanding of the functions of sleep.

Conclusion

In summary, we find little support for the ideas or evolutionary arguments set forth by Rial et al. Sleep with homeostatic regulation functionally linked to memory processing and plasticity is present in poikilothermic and homeothermic animals. Although Rial et al. acknowledge briefly that sleep functions other than simple rest could have evolved secondarily, they nevertheless conclude that sleep is an evolutionary junkyard of non-adaptation. Even if one disregards the direct evidence for a functional role of sleep other than inactivity, the inherent danger that animals assume by sleeping indicates that sleep must serve an important function.

Acknowledgements

This work was supported by the Max Planck Society.

References

1. Rial RV, Nicolau MC, Gamundi A, Akaârir M, Aparicio S, Garau C, et al. The trivial function of sleep. *Sleep Med Rev* 2007; **11**:311–25.
2. Stickgold R. Sleep-dependent memory consolidation. *Nature* 2005;**437**:1272–8.
3. Walker MP, Stickgold R. Sleep, memory, and plasticity. *Annu Rev Psychol* 2006;**57**:139–66.
4. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev* 2006;**10**:49–62.
5. Rattenborg NC. Evolution of slow-wave sleep and palliopallial connectivity in mammals and birds: a hypothesis. *Brain Res Bull* 2006;**69**:20–9.
6. Rial RV, Nicolau MC, Gamundi A, Akaârir M, Garau C, Aparicio S, et al. Comments on evolution of sleep and the palliopallial connectivity in mammals and birds. *Brain Res Bull* 2007; **72**:183–6.
7. Rattenborg NC. Response to commentary on evolution of slow-wave sleep and palliopallial connectivity in mammals and birds: a hypothesis. *Brain Res Bull* 2007;**72**:187–93.
8. Tobler I. Phylogeny of sleep regulation. In: Kryger MH, Roth T, Dement WC editors. *Principles and practice of sleep medicine*. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 77–90.
9. Hartse KM. Sleep in insects and nonmammalian vertebrates. In: Kryger MH, Roth T, Dement WC editors. *Principles and practice of sleep medicine*. 2th ed. Philadelphia: WB Saunders; 1994. p. 95–104.
10. Shaw PJ, Cirelli C, Greenspan RJ, Tononi G. Correlates of sleep and waking in *Drosophila melanogaster*. *Science* 2000; **287**:1834–7.
11. Hendricks JC, Finn SM, Panckeri KA, Chavkin J, Williams JA, Sehgal A, et al. Rest in *Drosophila* is a sleep-like state. *Neuron* 2000;**25**:129–38.
12. Sauer S, Herrmann E, Kaiser W. Sleep deprivation in honey bees. *J Sleep Res* 2004;**13**:145–52.
13. Hendricks JC, Williams JA, Panckeri K, Kirk D, Tello M, Yin JC, et al. A non-circadian role for cAMP signaling and CREB activity in *Drosophila* rest homeostasis. *Nat Neurosci* 2001; **4**:1108–15.

14. Joiner WJ, Crocker A, White BH, Sehgal A. Sleep in *Drosophila* is regulated by adult mushroom bodies. *Nature* 2006;**441**:757–60.
15. Pitman JL, McGill JJ, Keegan KP, Allada R. A dynamic role for the mushroom bodies in promoting sleep in *Drosophila*. *Nature* 2006;**441**:753–6.
16. Ganguly-Fitzgerald I, Donlea J, Shaw PJ. Waking experience affects sleep need in *Drosophila*. *Science* 2006;**313**: 1775–81.
17. Huber R, Hill SL, Holladay C, Biesiadecki M, Tononi G, Cirelli C. Sleep homeostasis in *Drosophila melanogaster*. *Sleep* 2004;**27**:628–39.
18. Rattenborg NC, Martinez-Gonzalez D. Avian slow-wave sleep homeostasis (APSS meeting abstract). *Sleep* 2007; in press.
19. Vyazovskiy VV, Borbély AA, Tobler I. Interhemispheric sleep EEG asymmetry in the rat is enhanced by sleep deprivation. *J Neurophysiol* 2002;**88**:2280–6.
20. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature* 2004;**430**:78–81.
21. Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ, et al. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat Neurosci* 2006;**9**:1169–76.
22. Huber R, Tononi G, Cirelli C. Exploratory behavior, cortical BDNF expression, and sleep homeostasis. *Sleep* 2007;**30**: 129–39.
23. Derégnaucourt S, Mitra PP, Feher O, Pytte C, Tchernichovski O. How sleep affects the developmental learning of bird song. *Nature* 2005;**433**:710–6.
24. Webb WB. Sleep as an adaptive response. *Percept Motor Skills* 1974;**38**:1023–7.
25. Meddis R. On the function of sleep. *Anim Behav* 1975;**23**: 676–91.
26. Lima SL, Rattenborg NC, Lesku JA, Amlaner CJ. Sleeping under the risk of predation. *Anim Behav* 2005;**70**:723–36.
27. Rattenborg NC, Amlaner CJ, Lima SL. Behavioral, neurophysiological and evolutionary perspectives on unihemispheric sleep. *Neurosci Biobehav Rev* 2000;**24**:817–42.
28. Rattenborg NC, Lima SL, Amlaner CJ. Facultative control of avian unihemispheric sleep under the risk of predation. *Behav Brain Res* 1999;**105**:163–72.
29. Mukhametov LM, Supin AY, Polyakova IG. Interhemispheric asymmetry of the electroencephalographic sleep patterns in dolphins. *Brain Res* 1977;**134**:581–4.
30. Lyamin OI, Mukhametov LM, Siegel JM. Relationship between sleep and eye state in Cetaceans and Pinnipeds. *Arch Ital Biol* 2004;**142**:557–68.
31. Lima SL, Rattenborg NC. A behavioural shut-down can make sleeping safer: a strategic perspective on the function of sleep. *Anim Behav*, in press.
32. Ruckebusch Y. The hypnogram as an index of adaptation of farm animals to changes in their environment. *Appl Anim Ethology* 1975;**2**:3–18.
33. Tobler I, Schwierin B. Behavioural sleep in the giraffe (*Giraffa camelopardalis*) in a zoological garden. *J Sleep Res* 1996;**5**:21–32.
34. Lesku JA, Roth II. TC, Amlaner CJ, Lima SL. A phylogenetic analysis of sleep architecture in mammals: the integration of anatomy, physiology, and ecology. *Am Nat* 2006;**168**: 441–53.
35. Sanford LD, Tang XD, Ross RJ, Morrison AR. Influence of shock training and explicit fear-conditioned cues on sleep architecture in mice: strain comparison. *Behav Genet* 2003;**33**:43–58.
36. Siegel JM. Clues to the functions of mammalian sleep. *Nature* 2005;**437**:1264–71.
37. Zepelin H, Siegel JM, Tobler I. Mammalian sleep. In: Kryger MH, Roth T, Dement WC editors. *Principles and practice of sleep medicine*. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 91–100.
38. Siegel JM. The REM sleep-memory consolidation hypothesis. *Science* 2001;**294**:1058–63.
39. Solodkin M, Cardona A, Corsi-Cabrera M. Paradoxical sleep augmentation after imprinting in the domestic chick. *Physiol Behav* 1985;**35**:343–8.
40. Alcock J. *Animal behavior*, 8th ed. Sunderland, MA: Sinauer Associates Inc; 2005.
41. Stephens DW, Krebs JR. *Foraging theory*. Princeton, NJ: Princeton University Press; 1986.
42. Mitchell WA, Valone TJ. The optimization research-program—studying adaptations by their function. *Q Rev Biol* 1990;**65**: 43–52.

Sleep Medicine Reviews (2007) **11**, 311–325

ELSEVIER

SLEEP MEDICINE reviews

www.elsevier.com/locate/smrv

THEORETICAL REVIEW

The trivial function of sleep ☆

Ruben Victor Rial*, María Cristina Nicolau, Antoni Gamundí, Mourad Akaârir, Sara Aparicio, Celia Garau, Silvia Tejada, Catalina Roca, Lluis Gené, David Moranta, Susana Esteban

Laboratori de Fisiologia, Institut Universitari de Ciències de la Salut, Universitat de les Illes Balears, 07122 Palma de Mallorca, Spain

KEYWORDS
Sleep evolution;
Rest–activity cycles;
Adaptation;
Evolutionary parsimony;
Evolution of consciousness

Summary Rest in poikilothermic animals is an adaptation of the organism to adjust to the geophysical cycles, a doubtless valuable function for all animals. In this review, we argue that the function of sleep could be trivial for mammals and birds because sleep does not provide additional advantages over simple rest. This conclusion can be reached by using the null hypothesis and parsimony arguments. First, we develop some theoretical and empirical considerations supporting the absence of specific effects after sleep deprivation. Then, we question the adaptive value of sleep traits by using non-coding DNA as a metaphor that shows that the complexity in the design is not a definitive proof of adaptation. We then propose that few, if any, phenotypic selectable traits do exist in sleep. Instead, the selection of efficient waking has been the major determinant of the most significant aspects in sleep structure. In addition, we suggest that the regulation of sleep is only a mechanism to enforce rest, a state that was challenged after the development of homeothermy. As a general conclusion, there is no direct answer to the problem of why we sleep; only an explanation of why such a complex set of mechanisms is used to perform what seems to be a simple function. This explanation should be reached by following the evolution of wakefulness rather than that of sleep. Sleep could have additional functions secondarily added to the trivial one, although, in this case, the necessity and sufficiency of these sleep functions should be demonstrated.

Introduction

In 1971, Rechtschaffen[1] stated that '*if sleep does not serve an absolute vital function, then it is the biggest mistake the evolutionary process ever made*'. Thirty-five years later, this statement remains unchallenged despite the lack of convincing evidence.

Abbreviations: DNA, deoxyribonucleic acid; FD, food deprivation; LH, learned helplessness; MOFS, multiorgan failure syndrome; RD, REM deprivation; RNA, ribonucleic acid; SD, sleep deprivation; TRD, total REM deprivation; TSD, total sleep deprivation

☆Authors contribution: M.C. Nicolau, A. Gamundi, M. Akaârir, S. Aparicio, C.Garau, S. Tejada, C. Roca, L. Gené and D. Moranta equally contributed to this report. R.V. Rial and S. Esteban led the redaction of the report.

*Corresponding author. Tel.: +34 97117347; fax: +34 971173184.
E-mail address: rvrial@uib.es (R.V. Rial).

1087-0792/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.smrv.2007.03.001

The most compelling arguments supporting the vital function of sleep are (1) the experiments of long-term total sleep deprivation (TSD), resulting in the death of experimental animals[2]; (2) the deleterious results of short-term sleep deprivation (SD) in cognitive functions; (3) the complexity of sleep, which most probably determined Rechtschaffen's assertion; (4) the supposed adaptiveness of many sleep signs; and (5) the existence of sleep regulation. In this review, we cast doubts on the demonstrative value of these five arguments.

In this review, the state of low activity observed in poikilothermic animals will be called 'rest'. Rest is an essential part of the activity–rest cycle of cold-blooded animals, and it has a well-acknowledged adaptive value.[3] The term 'sleep' will be reserved for mammals and birds. Sleep is also part of the activity–rest cycle, and shares a number of common features with the poikilotherms rest state. Therefore, rest and sleep should provide the organism with a similar primary function, and this is what we call the 'trivial function' of sleep. However, mammal and bird sleep shows a number of additional traits (e.g. two phases, changes in the activity of discrete central nervous system regions, in the regulation of physiological functions, in psychological efficiency). Therefore, the search for the function of sleep should be restricted to the differential traits of sleep. In other words, sleep should have two functional aspects: first, a (trivial) function common with rest; and second, a specific function related to the differential signs that are exclusive to sleep.

In addition to sleep, we will also review wakefulness. The adaptive value of rest might be understood only if the whole rest–activity cycle is taken into account. Similarly, the value of sleep is inseparably linked to that of waking. However, the use of the same word (waking) to describe the active part of the cycle of poikilotherms and homeotherms could be misleading because it implies homology between the waking of the two groups. However, the neuroanatomical control of wakefulness has suffered important changes in the evolution from poikilotherms to homeotherms. In functional terms, these changes have allowed the development of conscience, a function that is most probably impossible for a brain without a cortex. But no clear functional advance has yet been demonstrated in the transition from rest to sleep. In this situation, the principle of parsimony should favour hypotheses supporting the absence of any functional difference between rest and sleep, whereas the burden of the proof should be charged to the defender of additional functions.

Stress and sleep deprivation

Doubts about the specificity of the consequences of long-term TSD are not new, and some authors have suggested that TSD is simply a form of Selye's syndrome of adaptation.[4] However, Selye's syndrome is not the only condition causing lesions and death after exposition to unspecific stress. Here, attention will be devoted to theoretical considerations negating the usefulness of SD to provide evidence for the function of sleep. In addition, learned helplessness (LH) and multi-organ failure syndrome (MOFS) will be also discussed. LH can produce lesions and death, and also serious memory and learning deficits, whereas MOFS produces similar, albeit extremely variable, results. These examples will be used to explain first why different stressors (SD included) have life-threatening consequences, and second, why uncontrollable stress (including SD) causes cognitive deficits. Finally, the specificity of the impairments observed after SD cannot be used as a proof of the specificity of the causes.

TSD and total REM sleep deprivation (TRD) produce almost identical results,[2] which raises doubts about the general validity of the TSD experiments. These findings could be because (1) non-rapid eye movement (NREM) and rapid eye movement (REM) sleep have the same function; and (2) the set of symptoms produced after TSD and TRD are a consequence of similar unspecific stress. Although the first possibility must not be dismissed, it is evident that the longer survival of animals with TRD compared with TSD parallels a plausible lower amount of stress.

Sleep and food deprivation (FD): similarities and differences

The use of sleep-deprived animals to study the function of sleep comes from the widely accepted homeostatic regulation of sleep.[5] Accordingly, SD should be similar to the deprivation of other regulated needs (i.e. adequate food supply).

However, eating is an active behaviour and, within certain limits, hunger stress also enhances the activity of the animal, which increases the probability of discovering a suitable food source by means of a larger exploratory drive.[6] Therefore, food ingestion and hunger run in parallel, both inducing increases in activity. This is not so in SD experiments. Although the need for sleep always forces activity reduction, the animal must increase activity to avoid punishment. Therefore,

the sleep-deprived animal is always torn between two opposite needs.

Experiments on opposite drives, forcing an animal to be simultaneously active and inactive, have been repeatedly performed[7]; for instance, punishing access to food with a foot-shock. It is clear that these food-punishment experiments might not provide information on the function of the aliments but only on the effects of conflicting drives. However, such experiments are in fact quite similar to most SD procedures. Therefore, the theoretical foundation of SD experiments could be wrong and, in principle, might provide few clues on the function of sleep.

Learned helplessness and long-term sleep deprivation

LH was first defined by Seligman.[8] A typical LH experiment involves two animal groups. The control group receives escapable punishment (e.g. they can escape from a foot-shock by jumping to a safe compartment of the cage). The second group, 'helpless', receives exactly the same amount of punishment, but they cannot escape. Control animals readily learn to escape, whereas the helpless animals learn that there is no way to escape from the punishment, so that later, when offered the possibility, they do not even try to escape. In addition, they develop multiple lesions, infections, and eventually die.

Thus, TSD and LH seem to be similar in theoretical characteristics, in experimental procedure and in final results (Table 1). Many SD experiments impose a double punishment: a possible immersion in cold water and an unavoidable and stressful wakefulness. Each of them alone should be sufficient to produce LH, but administered together, they should produce LH at a fairly fast rate, fully agreeing with SD findings,[9] in which the rate of memory consolidation was inversely correlated to the stress produced by the experimental method to achieve SD.[10] This could have been deduced from recognizing the likely helplessness of sleep-deprived animals.

In spite of its deep implications, the association between the production of LH and SD consequences has received limited attention. Although several investigators have addressed the relationships between REM sleep and depression using inescapable footshock to produce LH as a model of depression,[11] only two reports have proposed that SD could be in fact a cause of LH.[12,13] It has been argued that the lesions produced after long-term SD and LH (and any other stress-mediated procedure) are different.[14] For instance, SD caused hyperphagia, ulcers in paws and tail and deep thermoregulatory disturbances. Although appetite is reduced, ulcers appear only in the stomach, and no thermoregulatory failure has been found in LH. However, it has been argued that these differences are a result of the methodological differences between SD and LH.[12,13] For instance, in normal LH, the punishment is always applied during waking, whereas, in SD, the punishment only occurs after effective sleep entrance. The normal waking behaviour is suppressed in LH, whereas this is not the case in SD, which causes overactivity of waking behaviours such as feeding. The production of gastric ulcers is similarly explained, as ulcers only develop in empty stomachs. In consequence, it is perhaps time to re-evaluate the research results relating sleep loss to physiological perturbations and memory consolidation.

Needless to say, the results should be different in human SD experiments. Although stress continues to be present, no cognitive helplessness should

Table 1 Similarities and differences between sleep deprivation and learned helplessness.

Sleep deprivation		Learned helplessness	
Treatments			
Controls	TSD animals	Controls	LH animals
Experimental stress	Experimental stress	Experimental stress	Experimental stress
Escapable wetting	Inescapable punishment: sleep loss, cold water wetting, or both	Escapable punishment (electric shock)	Inescapable punishment (electric shock)
Results			
No effects (normal sleep quota)	Sleep suppression; multiple lesions and death	No effects (normal learning capacity)	Helplessness, multiple lesions and death

LH, learned helplessness; TSD, total sleep deprivation.

occur, as humans always know that the experiment could end at will—they are in full control. This could explain, in part, the differences between human and animal SD.[15]

Multi-organ failure syndrome and total sleep deprivation

MOFS, first described in 1975 by Baue,[16] is well known in intensive-care units. Occasionally, after the recovery of an initial insult (e.g. major surgery, traumatic lesions, extensive burning), a rapid perturbation develops with a sequential or simultaneous implication of different organs and systems. Respiratory failure is the most frequent result, followed by a cascading failure of kidney, liver, cardiovascular, coagulation, central nervous system, and so on. Sepsis is considered the first trigger and the main cause of death, but it is not the only one, as tissular necrosis and inflammatory reactions are also frequent. The septic syndrome usually remains undetected in 50% of hemocultures, although postmortem analysis shows it in many organs.

The failure of organs with different tissular characteristics suggests that a common cellular insult is unlikely. The cascade of humoral and immune mechanisms starting after the first aggression is, in principle, adaptive but, when certain levels are surpassed, it goes out of control and, most probably, the same effector cells of the immune system cause multiple lesions and death.

MOFS and TSD are compared in Table 2. Although TSD outcomes have been attributed to MOFS,[25] only the possibility of bacterial invasion was analysed. In addition, the theoretical consequences of attributing the results of TSD to MOFS have been ignored, and a search of the most important bibliographic databases with 'multi-organ failure' and 'sleep' as keywords retrieves no results. However, the causes and consequences of MOFS could shed light on the consequences of TSD. As has been already explained, the final effects observed after TSD are not the same as those of experiments implying non-specific stress.[2,26] However, although MOFS is produced by non-specific causes, the number of failing organs is extremely variable, up to the point of being the main problem in defining the syndrome.[17] Thus, if a stressor ends producing respiratory insufficiency and another one renal failure instead, but both are included in MOFS, why should learned helplessness, causing gastric ulcerations and TSD causing ulcers in paws, and tail be considered different?

It is known that stress syndromes always follow the same general pattern.[27] During periods of abundance, organisms are able to optimize allocation of resources to achieve physiological adaptation (e.g. immune defence, metabolism, reproduction, somatic growth, attempting short-term welfare and long-term survival). However, when resources are limited, they are shunted between competing physiological demands, minimizing allocation to less essential functions. Thus, when confronted with a particular stressor, the organism must decide how to optimize the allocation of its resources for the new situation. Key factors are predictability and duration: stress spells of known and short duration are managed better. In these cases, the best strategy is to allocate most resources to fight against the stressor, whereas other maintenance functions can be resumed afterwards.[28] Considering SD as a stressor, short sleepless periods are probably usual in the natural life of rats, and clear strategies to cope with them should exist. On the contrary, long periods of TSD seem extremely unlikely in natural conditions. The same is evident for water immersion: mice[29] (and rats[30] too) are well used to swimming for short periods, but they despair in a few minutes when confronted with a long swimming period. Thus, rats under experimental TSD should fight against two chronic stressors for which no long-term strategy exists. However, there is no reason to expect exactly the same re-allocation of resources in, for example, LH, MOFS and TSD. This could explain the differences observed among them. It has been claimed[14] that the term 'stress' describes indiscriminately almost any insult to an organism or the responses to an insult and obscures functional information. In fact, stress syndromes produced by different stressors could show specific differences.[31] However, as the death cannot be solely attributed to the differential set of SD symptoms, but most probably to the complex interaction of a high number of factors, the usefulness of the stress concept as a general response of the organism to an environmental challenge should be maintained. In conclusion, the death observed after long-term SD is caused by multi-organ failure, a complex process caused by unspecific stress. Indeed, this could just be a tag to cover our ignorance. However, although no precise reason is given to explain the exact cause for the specificity of the lesions, we should rely on a unifying picture from which sleep and intensive care medicine could take advantage. Thus, for the time being, one feels compelled to continue relying on the unifying concept of stress.

Table 2 Comparing the effects of total sleep deprivation and multi-organic failure syndrome.

Effects of TSD[2]	Consequences of MOFS
Sleep-deprived rats die between 11 and 32 days	MOFS ceases with death after a few days[16]
Progressively debilitated animals, scrawny appearance with brownish and dishevelled fur	The patients turn debilitated and lank, a situation which has been called autocanibalism[17]
Severe and hyperkeratotic skin lesions localized on the tail and the plantar surfaces of the paws and the tail. The pathogeny of the lesions has not been solved	Frequent gastric ulcerations and necrotic haemorrhages in several organs. Sepsis is considered the main cause of death, but it is believed that lesions are not a direct consequence of the pathogenic agent. Instead, lesions are caused by the reaction of the organism[18]
Increased food intake: during the final quarter of survival the mean ingestion reached more than 80 and 100% above baseline levels	The metabolic expenditure is increased between 40 and 60%, and the nutritive needs are raised by the same amount,[19] although some authors[20] have observed a doubling of the energetic budget
A 20% reduction in weight loss in spite of increased food intake. The loss could not be explained by dehydration, malabsorption or gross perturbations of intermediary metabolism	Important weight loss in the second half of MOFS after a huge increase of metabolism[21]
Increase in energy expenditure, as calculated from the caloric value of food intake, weight change and wastes, and confirmed by indirect calorimetry. Mean energy expenditure during the final quarter of survival was more than twice baseline levels. It could not be explained by the metabolic cost of increased wakefulness, motor activity or water exposure. It was indicated and supported by an increase in heart rate in sleep-deprived rats	A hypermetabolic and hypercatabolic phase lasting 7–10 days is observed. During this phase glycolysis, glycogenolysis and muscular proteolysis are increased (autocanibalism)[21] concurrent with a reduction in protein synthesis. As a consequence, organ insufficiency begins
Body temperature was first increased, but in the second half of the survival period the temperature decreased	In the first phase (flow, reflow) O_2 consumption is reduced, accompanied by hypothermia (less than 36 °C) and vasoconstriction. This phase is followed by a phase of hyperthermia (flow) with body temperatures over 38 °C[22,23]
Plasma norepinephrine was increased	ADH, PL, ACTH, and GSH levels increased. Later, cortisol, glucagon, catecholamines and insulin increased.[24] When this phase remains uncontrolled, hypermetabolism is installed and perpetuated
A decrease in plasma thyroxin (T4) and an increase in the ratio of plasma T3/T4 was found in sleep-deprived rats	No studies of the the thyroidal state have been found. However, hypermetabolism, increased O_2 consumption, tachycardia and thermogenic changes strongly suggest a deep perturbation in the thyroidal state

MOFS, multi-organ failure syndrome; TSD, total sleep deprivation.

Short-term sleep deprivation

Perhaps, the most important difference between TSD and short-term SD lies in the absence of deleterious physiological imbalances in short-term SD. However, important cognitive deficits have been observed after short-term SD even in humans in whom no LH should occur. However, this does not mean a complete absence of stress. Quite the opposite, the prolongation of waking is always stressful, as everybody would attest. In consequence, the cognitive effects of short-term SD are also suspicious of stress contamination. In fact, it is known that, among other effects, stress causes modifications in the emotional state,[32] in arousal, in attention,[33] in decision speed,[34] in motor performance and memory formation[35] and

in retention,[36] i.e. it could be said that the consequences of stress and short-term SD are rather similar.

Is sleep always necessary? The evidence of sleep deprivation without stress

Long-term REM sleep suppression may be easily achieved by pharmacological procedures,[37] and thousands of people taking antidepressant medication are currently living with almost no REM sleep. Also, the absence of negative effects has been reported in the case of almost total REM sleep suppression resulting from brain lesions.[38] However, most surprisingly, TRD without adverse effects has been obtained in rats[39] by substituting REM sleep by waking periods of a similar average length. Additionally, in these experiments (1) the number of attempts to enter into REM sleep did not increase throughout the experiments; (2) no dissociation between REM elements was found; (3) no REM sleep rebound, and no increase in either ponto-geniculo-occipital spikes or in the number of eye movements was recorded after returning to normal conditions; (4) no increase in the production of emotional responses was registered; and (5) no reduction in cognitive performance was shown. Short-term sleep suppression has also been achieved using low stressing procedures, such as electrical stimulation in the receptive field[32,40] and in the hypothalamus.[41] These experiments also showed few consequences in the emotional and learning behaviour of the sleepless animals.

Experimental TSD has only been studied in a few species: humans, cats, dogs, mice, rats, and to a lesser extent, rabbits, guinea pigs and hamsters, from which the impossibility of long-term TSD has been assumed. However, naturally occurring long sleepless periods have been described in marine mammals[42] and in birds submitted to long periods of continuous light.[43] Important reductions in the amount of sleep without subsequent rebound have also been reported during adaptation to sleep laboratory in domestic herbivores,[44] in birds during the migration season,[45] in king penguins during the incubation and post-hatching periods when they must defend their extremely small (0.5 m^2) territory at a rate of about 5000 times per day.[46]

These cases have been disputed. It is assumed that dolphins can sleep while swimming.[47,48] True herbivores sleep[44] might have been replaced by drowsing. The presence of short sleep periods has also been shown in penguins.[48] However, we remark that these examples show that severe, and perhaps total, SD could occur without subsequent rebound or negative ill effects.

Recorded sleep durations of most laboratory and captive animal studies reflect maximal sleep capacity.[44] However, the minimal amount of sleep remains largely unknown for most animals. Undoubtedly, all animals *can* sleep, but this is not equivalent to saying that all animals *must* sleep; the assumption for a universal sleep need is, for the time being, unsupported. In fact, the number of sleepless cases, though small, is well comparable to the number of species in which the need for sleep has been demonstrated beyond any reasonable doubt, and this could mean that Mother Nature has resources to circumvent the need of sleep.

Interim summary 1: the existence of specific effects after sleep deprivation is disputable

The experiments of FD and SD cannot be compared. Pure FD causes no behavioural conflict, whereas these are unavoidable in SD. Therefore, the theoretical foundation of TSD is probably wrong and the results suspicious.

The results of unspecific stress are extremely variable. There is no reason to expect the same lesion or cognitive deficit after the application of different chronic and acute stressors. Thus, the existence of minute differences do not prove the absence of a general common mechanism.

The comparable results of LH and SD, and the well-known effects of stress on anxiety, arousal, attention, memory and learning, question the hypothesis that sleep serves to restore cognitive functions.

The similar results of rotating disk TSD and TRD, in contrast with those provoked by other methods of REM sleep suppression, further suggest that SD experiments by the rotating disk method are flawed.

The existence of spontaneously occurring long periods of sleep suppression or reduction in mammals and birds suggest that the need of sleep is not universal.

The adaptive function of sleep could be non-existent

The absence of adaptation is the null hypothesis

Williams[49] observed in 1965 that adaptation is an onerous concept that should not be called in

absence of positive proof. The lack of adaptation is parsimonious, and should be always considered as the null hypothesis in absence of definite counter-proof, without need of demonstration.

The non-coding, deoxyribonucleic acid (DNA) as a metaphor for the non-adaptive value of sleep

The belief in the adaptive value of sleep is probably sustained by the so-called argument of complexity,[50] also used, for instance, in the belief of the adaptive value of the eye: such a complex organ would require co-adaptation of multiple structures and sub-functions, and it could have appeared only if every component co-operates with the rest to fulfil a unique, well-defined and adaptive function.[51] However, complexity is not by itself firm proof of adaptation. A well known, complex, but seemingly useless structure, could be invoked as a metaphor for the uselessness of many sleep signs. There are two types of DNA in live beings: coding segments with clear functionality, and non-coding DNA. Coding DNA is usually transcribed to RNA and translated into functional proteins. However, there exists a large proportion of DNA without coding function.[51] Several hypotheses have attempted to explain its presence in the cellular nucleus[52,53] and, in fact, variable amounts of protein coding, transcribed non-coding and non-transcribed DNA regions have been identified in different species.[54] Owing to its apparent lack of function, the non-coding DNA first received the names of 'nonsense' or 'junk', although nowadays 'non-coding DNA' or 'scrap-yard DNA' are preferred. However, it is of interest that (1) the variability of DNA ranges from 1–3000 in animals[55]; (2) individuals of the same species, as shown by human fingerprinting studies, show a huge variation in the number of long repeating DNA sequences immune to point mutations and without known phenotypic consequences; and (3) no phylogenetic correlation has been found with the amount of DNA.[55] These three traits could be compared replacing DNA with the amount of REM sleep: (1) it ranges from zero[56] to 60% of total sleep time in different animals[57]; (2) there are important inter-individual variations within the same species; and (2) it also lacks any significant phylogenetic correlation.[58] Thus, if geneticists readily accept neutral genes,[59] why has no sleep researcher ever considered REM sleep absence of function, for instance? Is the non-coding DNA another big mistake of Mother Nature?

The primary function of DNA is protein coding, whereas the duplication of DNA segments is, most probably, an important evolutionary step to achieve protein diversification. Non-coding fragments of DNA could also have reached important regulatory functions. However, it is well recognized that these new functions are secondary adaptations for old evolutionary remnants.[53,55] The same could have occurred with many sleep traits.

The environmental pressure during waking has directed the evolution of sleep

Most definitions of sleep consider motor rest as an essential component. When rest is absent, common sense suggests that sleep should be negated. When motor rest is spontaneously reduced, for instance in birds' migrating season, the reduction in sleep is immediately assumed.[45] The cetaceans swimming movements never stop. However, evident electrographic signs of sleep have been found. Therefore, sleep without motor rest seems to exist. However, although light sleep might be bihemispheric, deep sleep is always unihemispheric.[48] Thus, the active hemisphere is seemingly in charge of motion control, and the activity during sleep does not disprove the likely absence of motor output from the sleeping hemisphere.

Some researchers consider that reduced sensory sensitivity is a fundamental component of sleep, with precedence over motor rest.[60] However, sleeping herbivores seem to have a permanently high sensory sensitivity.[61] Van Twiver and Allyson[62] ascertained increases in sensory thresholds of sleeping pigeons, but their report shows an apparent non-significant difference between waking and slow wave sleep in three of the four animals studied. Moreover, the authors stated that the animals 'were very reactive and easily disturbed in the laboratory. The slightest sound or movement often was sufficient to arouse from sleep' and 'it was never possible to directly observe the sleeping pigeon without alerting it'. Thus, exceptions in the increased sensory threshold could also exist.

In addition, asserting the presence of sleep in animals engaged in motor activity seems a contradiction in terms, a perversion of language. A philosophical discussion on the 'essence' of sleep is beyond the scope of this review, but it is enough to recognize that the relative importance of sensory thresholds and motor rest is debatable. In fact, the aim of this review is to show that many ideas on sleep are taken for granted without adequate discussion.

Accordingly, three simple mechanisms should be necessary to provide the postulated need of motor rest: (1) ability to select a secure resting place;

(2) a switch to block activity; and (3) a mechanism to reduce the sensitivity to irrelevant stimulus.

However, it is evident that rest and activity, and also sleep and wakefulness, are two faces of the same coin, i.e. they show an absolute and perfect inverse correlation. If an animal has, for instance, 8 h of total sleep time, it also has, undoubtedly, $24-8=16$ h of wakefulness. Thus, if some physiological variable shows a good correlation with sleep, exactly the same correlation with wakefulness can be stated (with in fact opposite sign). Though evident, this is seldom recognized, and over a dozen reviews have studied correlations between total sleep time and environmental, constitutional and ecological parameters, ignoring that the same correlations must exist with waking.[63]

Thus, in pursuing a full debate on the function of sleep, the following discussion will propose that most of the traits generally ascribed to sleep in essence concern waking instead. Waking has much higher precedence than sleep in the adaptation of animals, as most (if not all) vital needs are fulfilled during waking (e.g. alimentation, defence, reproduction, social interactions). Therefore, natural selection must have caused an extremely strong pressure on waking. Instead, we will try to show that sleep practically lacks phenotypic traits on which pressure could have been exerted.

Selectable sleep traits: do they really exist?

Sleep has a vast array of signs: almost every physiological function changes after sleep onset (e.g. electroencephalogram, state of eyes, muscular tone, cardiac activity, autonomic function, respiratory physiology, reflexes, psychological variables…). Also, sleep shows two phases with highly differentiated brain activity. Altogether, sleep seems to be a rather complex behaviour. Thus, it could be argued that these components could have been submitted to selective forces as important as those that modelled waking. This argument may take several forms: (1) animals lacking some particular sleep sign were just extinct because they lacked the function provided by the sign that they lack. Therefore, the sign under question should have adaptive value. Response: apart from being circular, the Williams criteria[50] should be applied: when conclusive evidence is lacking, adaptation should not be invoked; (2) environment seems to have placed strong pressure on total sleep time or sleep intensity, resulting in the extreme variation found in different animals.[63] Response: the claimed variations in sleep intensity do not affect sleep, but waking instead. There are no light, deep, long and short sleepers, but animals with variable waking length and efficiency. When a sleeping animal is threatened, it does not attempt a change of sleep stage; on the contrary, it immediately tries to awake in order to cope with the alarming stimulus.[64] In short: waking is important; sleep is what animals do when they have nothing to do; (3) differences exist in the amount of NREM and REM sleep of young and adult animals, and should be the result of natural selection. Response: the correlation between age and sleep is evident, but no causal relationships may be deduced from correlations. The high amount of sleep in the immature brain has been always considered necessary for brain development. However, the relation can be the opposite: a high amount of purposeless sleep could be a mere consequence of immaturity, just as immobility is a consequence of an immature motor control. It seems evident that a much larger amount of brain is needed to cope with the environmental challenges during waking than during sleep. The only possibility for an immature brain lies in resting in a secure environment, be it in the uterus or the nest. This proposal has always been neglected, in spite of being parsimonious. In comparison, the development-promoting hypothesis is onerous; (4) the amount of sleep is related to the metabolic needs of the species. Therefore, it should have been selected to save energy. Response: the main determinant of specific metabolism is body size. Small animals have higher metabolic needs.[65] Therefore, they need more waking time to gain access to and eat the food they need. Thus, increased amounts of waking could have been selected instead of reduced sleep.

The list just reviewed is not exhaustive, but shows that it could be disappointingly difficult to find significant selectable unique signs of sleep. Sleep always seems to be rest and has very low behavioural output. In an old joke, a customer asks for a hot dog without mustard. To which the waiter replies: 'Sorry Sir, we have finished the mustard. Would you mind taking it without ketchup?' Just as non-existent mustard cannot be selected, Mother Nature could not select non-existent traits. Most phenotypic traits generally attributed to sleep are in fact factors modulating activity, the truly important force driving most signs of sleep.

The regulation of sleep

Circadian regulation is characteristic of sleep and simple rest. It is universal, from unicellular organisms to animals and plants, and nobody doubts the

adaptive value of the time division in rest–activity periods.[3] Homeostatic regulation of sleep also exists, but it is believed to be modern in front of the circadian one. Hence, homeostatic regulation seems to be a true sleep sign that should have been selected. This contradicts the supposed absence of phenotypic sleep traits defended here. To argue against this statement, the homeostatic regulation will be separately analysed in homeotherms and poikilotherms.

Homeostatic regulation in poikilotherms

The homeostatic and circadian regulation of rest and activity seems to be opposite in poikilotherms, as homeostasis could determine rest during the inconvenient part of the geophysical cycle.[66] In spite of this, it has been found that rest and sensory thresholds are increased after forced activity in both poikilotherm vertebrates and invertebrates.[67] Therefore (1) the rest of poikilotherms could be independent of circadian cycles; (2) the homeostatic regulation observed in these animals could be a sign belonging to rest and not to waking; and (3) the homeostatic regulation of rest in poikilotherms could have been the seed for the development of homeostatic regulation of sleep in homeotherms.

However, it can be argued that the experiments of rest deprivation may have recorded fatigue instead of a true rest rebound. A number of different types of fatigue have been recognized (e.g. muscular, sensory, central…[68]) but they are independent of rest, which appears spontaneously beside increased exertion, meaning that it is internally driven. The confusion between fatigue and internally driven rest was avoided in only one study. In a first experiment, lizards submitted to a long period of continuous light showed a reduced activity when light–dark alternation was restored, which could have been due to fatigue as in other experiments. But a second experiment showed that the activity was increased after a long period of continuous dark (and rest), a result that in no way could be attributed to fatigue. However, this experiment also demonstrated that the homeostatic regulation of poikilotherms was not opposite to the circadian one, because the increase in activity was strictly bound to the light period (i.e. the increased activity never invaded the dark time).[69] Once again, the benefits of the regulation concern activity and not rest. This conclusion agrees with earlier studies showing that reptiles have no problem in remaining hidden in their burrows during several days, which means that the amount of rest is not regulated. Instead, the amount of activity is carefully controlled depending on environmental (e.g. temperature, insolation, availability of food, predation danger) and internal (e.g. fat reserves, reproductive state) factors. The decision to turn active depends only on the balance between the benefits and costs of maintaining activity.[70] In summary, the supposed homeostatic regulation of rest in poikilotherms most probably is either mere fatigue or regulation of waking. In either case, a true homeostatic regulation of rest could be non-existent. Let us remark that this proposition is parsimonious: it simply rejects the need to explain rest.

Homeostatic regulation in homeotherms

If poikilotherms lack regulation of rest, the homeostatic regulation of sleep should have appeared 'ex novo' in homeotherms. However, homeothermy could have allowed continuous activity, which on the other hand reduces the fitness provided by well-adjusted rhythms. Therefore, new mechanisms should have developed to counteract the permanent activity allowed by homeothermy. Surprisingly, Mother Nature seems to have produced just the opposite, as the homeostatic regulation seems to impose further difficulties in attaining circadian regulation. When sleep deprived, we want to sleep at all costs, even if it is the wrong time of the day. In consequence, the only explanation for the homeostatic regulation of sleep seems to lie in the existence of a vital function of sleep.

We propose here that the two regulatory modes are not opposite. Instead, homeostatic regulation could have worked to ensure the circadian rhythms when they were endangered after thermal independence. A huge amount of data (e.g. on shift work) shows that it is practically impossible for humans to maintain a permanently inverted circadian sleep schedule. In consequence, one should conclude that the homeostatic pressure towards sleep only works on a short-term schedule, whereas the circadian regulation always takes precedence in the long term. Thus, homeostatic and circadian regulation could not be truly considered as opposite. In addition, it seems likely that short-term physiological regulatory mechanisms can be more easily developed, whereas long-term controls are more difficult. The evident and immediate consequences of sleep neglect constitute a powerful drive to obtain immediate (homeostatic) sleep recovery; on the other hand, the low quality of

the attained diurnal sleep should work against repeating the sleepless episode. Short-term homeostasis could thus be an immediate solution to ensure a long-term circadian regulation. As in poikilotherms, this proposal is parsimonious: sleep continues being for rest, and nothing else should be hypothesized without explicit proof.

Interestingly, the relative importance of homeostatic and circadian regulation of mammals and birds differs. Homeostatic regulation of sleep in birds has been challenged[71]; however, birds maintain an extremely sophisticated circadian control, with pineal and deep brain photoreceptive sensitivity.[72,73] They have circadian clocks in the hypothalamus, but also in the retina[74–76] and in the pineal gland.[77,78] Thus, although mammals have homeostatic and circadian controls, birds have an enhanced circadian control but poor homeostatic regulation.

A possible explanation stems from the differences in chronotype. Birds are primarily diurnal, a trait inherited from reptiles, absolutely dependent on external heat sources. Instead, mammals are primarily nocturnal, a mode of life that was only possible after the development of homeothermy.[79] In consequence, the first proto-mammals had to fight against the primary rest-promoting effects of darkness, which should have imposed a reduction in the importance of the circadian control. The differences are also reflected in the different regulation modes of the two groups: for instance, avian sleep relies heavily on melatonin,[80] the main circadian effector, whereas mammals have had to develop a new mechanism to support the weakened circadian regulation. This is how the mammalian homeostatic control of sleep could have developed, to reinforce the circadian rest–activity cycles when they were at risk of being lost with the advent of homeothermy and nocturnal lifestyle.

The difference between non-rapid eye movement sleep and rapid eye movement sleep

Although the complexity provided by the existence of two phases and their variable amounts has already been discussed, their mere existence constitutes a challenge for any hypothesis trying to explain the function of sleep. This is the purpose of the following lines.

Evolution proceeds along two paths. A given structure could diverge to allow different functions in different species. This is the case of the mammalian limb, which allowed terrestrial animals to walk while evolving to support swimming of aquatic animals. New structures with new functions could also be developed, but sometimes a new structure could converge to achieve adaptations similar to others already in existence. This -is the case with bats' forelimbs, which converged to wings analogous to those of birds. Starting from different functions, both converged to become one.

NREM and REM sleep could have also resulted from either convergence or divergence. However, their extremely different neuroanatomic control makes it almost impossible to imagine a common origin and a later divergence. With convergence, however, both share an evident phenotypic trait despite their different structural basis: they are just sleep. No functional difference has been convincingly demonstrated.

It has been necessary to develop extremely sophisticated instruments to discover the existence of the two phases. Discovering the phenomenology of sleep has been a task almost as difficult as discovering the non-coding DNA. Thus, both could have reached their present complexity while remaining hidden from selective forces as much as they have remained hidden from researchers until a few years ago. As a mental experiment, how would a farmer succeed in obtaining a strain of animals with a high amount of REM sleep? Would it be possible without a polygraph? The success seems hardly believable in spite of the extremely high efficiency of artificial selection. Then, how would the much less efficient natural selection be performed? Mother Nature seems to have made a tremendous effort to hide the difference between NREM and REM sleep. Both are just sleep. Once again, this proposition is parsimonious. Searching for a mysterious functional difference between NREM and REM sleep is equivalent to searching for differential functions of bats and birds wings.

Interim summary 2: most traits currently attributed to sleep could have no real significance

The most important traits of sleep/rest are the ability to choose a suitable resting site, the switching off of motor activity and sensitivity to irrelevant sensory inputs.

Waking has higher precedence in adaptation than sleep, which could be no more than rest. Most supposed sleep traits are likely to be waking traits instead.

No firm demonstration of rest regulation in poikilotherms has been reported. Instead, careful regulation exists for the amount of activity. The homeostatic regulation of sleep in homeotherms could simply serve as a first step to ensure the long-term time division into sleep and waking.

In spite of neuroanatomical and physiological differences, NREM and REM sleep show no phenotypic differences. They should be the result of evolutionary convergence and they could exist without primary functional differences.

Many traits of sleep could be evolutionary remnants of earlier waking

As it has already been remarked, most non-coding DNA proceeds from earlier coding genes. Similarly, an important number of sleep traits could be remnants of earlier waking adaptations, which were turned into non-waking after the development of more efficient wake mechanisms.[81,82]

Reptiles have an extremely small associative multisensory cortex,[83,84,] without capability to sustain consciousness.[85–87] Instead, their main sensory projections are independent and distributed along the brain axis. For instance, vision is placed in the mesencephalic tectum, whereas audition is placed in the istmus. Although reptiles can perform efficient visual and auditive analyses of the environment, their ability to produce a composite, multisensory image of the world is limited. They also lack telencephalic motor centres. Instead, the reticular formation constitutes their final common path,[88] and the different sensory systems should compete to produce motor output.[85] Although the isolated mammalian forebrain can show transitions between waking and sleep,[89] the reptilian waking is entirely dependent on the activity of subtelencephalic regions.[83,84] In consequence, the homology between reptilian and mammalian waking should be questioned, and this has led us to propose that they are not homologous, but analogous,[81,82] having converged to fulfil the same function but with different neurological substrates and independent evolutionary history. When evolving from reptiles to mammals, ancient non-cortical waking should have been abandoned ahead of the modern mammalian one. The waking structures of the brainstem must have suppressed their sensitive and motor capacity, and the regression of the mesencephalic optic tectum is an outstanding example. Most of these remnants constitute the sleeping brain after the atrophy of their previous waking function. Sleep could thus be a junkyard, just like an important portion of DNA. Although they could have developed secondary functions, both share a number of earlier functional traits, which were turned into silenced remnants, unnecessary after the development of more efficient substitutes.

Why we sleep

The causes of a process can be classified as immediate, proximal and final. The immediate cause of sleep could be any change in the internal or external environment causing immediate sleepiness. The proximal cause should be the homeostatic maintenance of some function, whereas the final cause aims to explain why, when and how the process appeared. Indeed, only the last two types are truly considered as causes of sleep. An example of proximal cause is the proposition that the purpose of sleep is for cognitive maintenance, whereas the third type intends to explain the evolution of sleep.

Interest in the relationships between sleep and cognitive processes is increasing. A problem with the related studies lies in the huge amount of different mechanisms involved. Great advances in the knowledge of memory and learning mechanisms have been made, but the difficulty in reaching conclusions increases several orders of magnitude if these mechanisms are evaluated after having suffered an experimental modification in sleep, most probably contaminated with stress. In addition, every type of learning depends on motivation, arousal, attention, and memory, a complex set of factors undoubtedly sensitive to stress.

Even if the problems with stress contamination are fixed, the evidence provided so far might not be insufficient to demonstrate a causal relation between sleep and cognitive processes. The validity of a hypothesis does not depend on the amount of empirical evidence supporting it, as a single fact could be sufficient to falsify a hypothesis. The empirical proof sustaining that the earth is flat is unlimited but a single fact is enough to show that the earth is not flat. Let us remember that no relation between brain size and sleep exists, that the evidence supporting the memory consolidating effects of sleep is contradictory, and that if sleep serves to consolidate learning, a cat should sleep less than 10% of the 8 h that human beings sleep.

Additional arguments could also be proposed. Let us suppose that the causal relationship between

sleep and cognitive maintenance is demonstrated by firm and uncontested evidence. In this case, a fundamental question would still remain: why the eventual process could only be achieved during sleep and not during waking?

It has been argued that the memory consolidation effects of sleep are not necessarily 'all-or-none': '*in the absence of REM sleep, when the most effective memory maintenance mechanisms fail (those of NREM sleep followed by REM sleep), the memory falls back on its underlying "safeguards"—the primitive mechanisms of NREM sleep alone*' to continue: '*this is not to imply that various amounts of brain processing … of memories do not continue during waking …*'[90] It is puzzling to see a statement that the function of REM sleep is memory maintenance, but NREM is also deemed necessary and, finally, memory may also continue being processed during waking. If this is so, why should sleep exist if the same result can be attained during waking? This is another example of non-parsimonious thinking.

The hypothesis sustaining cognitive functions for sleep seems to have rather limited validity. The same could also be said of most proposed proximal causes of sleep. In general terms, a cause should always explain that sleep is necessary and sufficient to produce the proposed effect, and, when some exception is found, why it works in some species and not in others. Moreover, sleep signs are numerous, and an interested researcher could investigate the cause for each one. Additionally, sleep variability is immense, and research should be carried out for every sleep sign in every species. As a result, disentangling every cause of each of the eventual signs could be a hopeless task. The situation could in fact be similar to that which caused the abandonment of Lamarkism as an evolutionary theory. Lamarkism was not rejected as a result of discovering a solid counterproof, but rather because of lack of any positive evidence, in spite of the high verisimilitude of its reasoning. The huge research effort devoted to answer the big why we sleep question has generated very scant positive evidence.

On the other hand, this review has shown that (1) experiments relating to SD raise many reasonable doubts about the specificity of the results claimed; (2) the evidence provided by the arguments of design for the existence of sleep adaptation is weak; (3) sleep has quite a low number of phenotypic traits to which natural selection could have exerted pressure; and (4) most sleep-specific traits proposed so far could be claimed as belonging to waking. Thus, proof that justifies the existence of a proximal function for the complex set of signs of the mammalian sleep are rather weak. In consequence, the principle of parsimony forces us to use the simplest hypothesis. The universality of the rest–activity cycles, as well as their undisputed selective value[3] constitutes the parsimonious alternative for the proximal function of sleep.

In addition, this review also provides an explanation of why evolution has produced the sleep of mammals and birds. Of course, evolutionary hypotheses cannot avoid remaining in the realm of speculation: sleep leaves no fossil remnants, and no direct testimony of evolution will ever exist. As a consequence, they should rely on hints provided by comparative and embryological studies submitted to strong principles of logic and epistemology. Among them, the principle of parsimony is essential.

However, sleep could still have secondary functions besides maintaining rest during part of the geophysical cycle. Quite often, evolution has reused old structures for new functions. Examples are the use of the respiratory system for acoustic communication; the skeletal bones first developed as a calcium store, and the new use of the fish jawbones in the middle ear of mammals. However, with sleep, animals began resting during one half of the geophysical cycle and then, multiple and even vital functions could have been secondarily developed in different mammals. Sleep could have ended with a single primitive function but also with many secondarily developed ones.

Conclusion: sleep is a junkyard in the evolution towards cortical conscience

Mammalian sleep has no function apart from the rest of simple organisms; this most likely represents its 'absolute vital function', as Webb[91] and Meddis[92] proposed many years ago. So, the problem of why we sleep only lies in explaining the complexity of the polygraphic sleep of homeotherms in front of the mere rest of simpler animals. Undoubtedly, sleep began as behavioural arrest; however, its essential function did not change when it acquired a number of bizarre traits. And so it remains, far from showing a simple and straightforward aspect. The structure and function of the nervous system has evolved as an immensely complex patchwork in which cellular aggregations developed, were discarded and reused time and again for many different—and even opposite—functions, and this may be the case for sleep, a junkyard full of discarded remnants produced along the development of cortical conscience.

Practice points

- The supposed complexity of mammalian sleep could be unimportant. There are plenty of complex structures and functions, which, from an engineer's point of view, could have developed, in a simpler and straightforward form.
- Sleep could be no more than an inactive state, with few differences from the rest of simple animals. However, many secondary functions may have developed in addition to the primary function of sleep.

Research agenda

- Imaginative, additional experimental procedures to achieve sleep deprivation without stress contamination should be developed.
- It is necessary to re-evaluate past experiments in order to relate sleep and memory or learning to take into account the likely production of learned helplessness.
- Experimental research on animals and human beings should continue until a complete understanding of why and when every phenomenologic trait of sleep is reached.

Acknowledgements

This work has been performed thanks to a grant from the Ministerio de Ciencia y Tecnología of the Spanish Government Number BFI2002-04583-C02-02.

References

1. Rechtschaffen A. The control of sleep. In: Hunt WA, editor. *Human behaviour and its control*. Cambridge, MA: Schenkman; 1971.
2. Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. Sleep deprivation in the rat, X: integration and discussion of the findings. *Sleep* 1989;**12**:68–87.
*3. Aschoff J. Survival value of diurnal rhythms. *Symp Zool Soc London* 1964;**13**:79–98.
4. Feinberg I. Delta homeostasis, stress and sleep deprivation in the rat: a comment on Rechtschaffen et al. *Sleep* 1999;**22**:1021–4.
5. Borbély AA. A two-process model of sleep regulation. *Hum Neurobiol* 1982;**1**:195–204.
6. Pierre PJ, Skjoldager P, Bennet AJ, Renner MJ. A behavioral characterization of the effects of food deprivation on food and non-food object interaction: an investigation of the information gathering functions of exploratory behavior. *Physiol Behav* 2001;**72**:189–97.
7. Asrin NH. Punishment and recovery during fixed-time performance. *J Exp Anal Behav* 1959;**2**:301–5.
*8. Seligman MEP. Chronic fear produced by unpredictable shock. *J Comp Physiol Psychol* 1968;**66**:402–11.
9. Vertes RP, Eastman KE. The case against memory consolidation in REM sleep. *Behav Brain Neurosci* 2000;**23**:867–76.
10. Coenen A, Van Luijtelaar ELJM. Stress induced by three procedures of deprivation of paradoxical sleep. *Physiol Behav* 1985;**35**:501–4.
11. Adrien J, Maudhuit C, Martin P. Antidepressant-like effects of paradoxical sleep deprivation in the helpless paradigm. In: *Founding Congress of the World Federation of Sleep Research Societies*, Cannes, 1991, p. 452.
12. Rotenberg VS. sleep and memory, I: the influence of different sleep stages on memory. *Neurosci Biobehav Rev* 1992;**16**:497–502.
13. Rotenberg VS. Sleep after immobilization stress and sleep deprivation: common features and theoretical integration. *Crit Rev Neurobiol* 2000;**14**:225–31.
14. Rechtschaffen A, Bergmann BM. Sleep deprivation in the rat by the disk-over-water method. *Behav Brain Res* 1995;**69**:55–63.
15. Bonnet MH. Sleep deprivation. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 3rd ed. Philadelphia: WB Saunders; 2000.
16. Baue AE. Multiple, progressive or sequential systems failure. A syndrome of the 1970s. *Arch Surg* 1975;**110**:779–81.
17. Ibáñez J. *Síndrome de Fracaso Multiorgánico*. Barcelona: Editorial MCR; 1992 [in Spanish].
18. Balk RA, Rone RC. The septic syndrome: definition and clinical implications. *Crit Care Clin* 1989;**5**:1–8.
19. Barton R, Cerra FB. The hypermetabolism: multiple organ failure syndrome. *Chest* 1989;**96**:1153–60.
20. Bouffard Y, Viale G, Delafosse BJP, Annat G, Guillaume C, Motin J. Energy expenditure in the acute renal failure patient mechanically ventilated. *Intensive Care Med* 1987;**13**:401–4.
21. Little RA, Campbell IT, Green CJ. Nutritional support in acute renal failure in the critically ill. In: En Bihari D, Neil G, editors. *Acute renal failure in the intensive therapy unit*. Berlin: Springer; 1990. p. 771–9.
22. Cerra FB, Siegel JH, Colman B. Septic autocanibalism, a failure of exogenous nutritional support. *Ann Surg* 1980;**192**:570–4.
23. Sánchez JM. Soporte nutricional durante el fallo multiorgánico. In: Ibáñez J, editor. *Síndrome de fracaso multorgánico*. Barcelona: Editorial MCR; 1992. p. 63–78 [in Spanish].
24. Murillo F, Muñoz MA, Domínguez JM, Maestre A. Fallo multiórgano y trauma. Prevención y tratamiento. In: Ibáñez J, editor. *Síndrome de fracaso multorgánico*. Editorial MCR Barcelona; 1992. p. 91–100 [in Spanish].
25. Bergmann BM, Gilliland MA, Feng PF, et al. Are the physiological effects of sleep deprivation in the rat mediated by bacterial invasion? *Sleep* 1996;**17**:554–62.
26. Rechtschafen A, Bergmann BM. Sleep stage priorities in rebounds from sleep deprivation: a response to Feinberg. *Sleep* 1999;**22**:1024–30.
27. Sandland GS, Minchella DJ. Costs of immune defense: an enigma wrapped in an environmental cloak? *Trends Parasitol* 2003;**19**:571–4.

*The most important references are denoted by an asterisk.

28. McNamara JM, Buchanan KL. Stress, source allocation and mortality. *Behav Ecol* 2005;**16**:1008–17.
29. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for antidepressants. *Arch Int Pharmacodyn Ther* 1977;**229**:327–36.
30. Paré WP. Behavioral despair test predicts stress ulcer in WKY rats. *Physiol Behav* 1989;**46**:483–7.
31. Velazquez-Moctezuma J, Dominguez-Salazar E, Cortes-Barberena E, et al. Differential effects of rapid eye movement sleep deprivation and immobilization stress on blood lymphocyte subsets in rats. *Neuroimmunomodulation* 2004;**11**:261–7.
32. Kowalzon VM, Tsibulsky VL. REM sleep deprivation stress and emotional behaviour in rats. *Behav Brain Res* 1984; **14**:235–45.
33. Eisenk MW. Attention. In: French CC, Colman AM, editors. *Cognitive psychology*. London: Longman; 1995.
34. Plowright CMS, Shettleworth SJ. Time horizon and choice by pigeons in a prey selection task. *Anim Learn Behav* 1991;**19**:103–12.
35. Cabib S, Castellano C. Impairments produced by amphetamine and stress on memory storage are reduced following a chronic stressful experience. *Psychopharmacology* 1997;**29**: 161–7.
36. Diamond DM, Rose GM. Stress impairs LTP and hippocampal dependent memory formation. *Ann N Y Acad Sci* 1994; **746**:411–4.
37. Viot-Blanc V. Biological models of depression: effect of antidepressants on sleep. *Encephale* 1995;**7**:35–40.
38. Lavie P. Localized pontine lesion: nearly total absence of REM sleep. *Neurology* 1984;**34**:118–20.
*39. Oniani T, Lortkipanidze N. Effect of paradoxical sleep deprivation on the learning and memory. *Neurobiol Sleep Wake Cycle* 2003;**3**:9–43.
40. Lucas EA. Effects of five to seven days of sleep deprivation produced by electrical stimulation of the midbrain reticular formation. *Exp Neurol* 1975;**49**:554–68.
41. Detari L, Kukorelli T, Hajnik T. Long term sleep deprivation by hypothalamic stimulation in cats. *J Neurosci Methods* 1993;**49**:225–30.
*42. Lyamin O, Pryaslova J, Lance V, Siegel JM. Animal behaviour: continuous activity in cetaceans after birth. *Nature* 2005;**435**:1177.
*43. Berger RJ, Phillips NH. Constant light suppresses sleep and circadian rhythms in pigeons without consequent sleep rebound in darkness. *Am J Physiol Regul Integr Comp Physiol* 1994;**36**:R945–52.
44. Campbell SS, Tobler I. Animal sleep: a review of sleep duration across phylogeny. *Neurosci Biobehav Rev* 1984;**8**: 269–300.
45. Rattenborg NC, Mandt BH, Obermeyer WH, Winsauer PJ, Wikelski M, Benca RM. Migratory sleeplessness in the white-crowned sparrow (*Zonotrichia leucophys gambelii*). *PloS Biol* 2004;**2**:924–36.
46. Jouvet M. *The paradox of sleep*. Cambridge MA: MIT Press; 1999.
47. Pilleri G. The blind Indus dolphin. *Platanista ind. Endeavour* 1979;**3**:48–56.
48. Dewasmes G, Loos N. Diurnal sleep depth changes in the king penguin (*Aptenodytes patagonicus*). *Polar Biol* 2002;**25**:7.
49. Williams GC. *Adaptation and natural selection: a critique of some current evolutionary thought*. Princeton: Princeton University Press; 1966.
50. Dawkins R. *The blind watchmaker*. London: Penguin; 1986.
51. Nei M. Gene duplication and nucleotide substitution in evolution. *Nature* 1969;**221**:40–2.
52. Makalowski W. Genomic scrap yard: how genomes utilize all that junk. *Gene* 2000;**259**:61–76.
53. Gregory TR, Hebert PDN. The modulation of DNA content: proximate causes and ultimate consequences. *Genome Res* 1999;**9**:317–24.
54. Shabalina S, Spiridonov NA. The mammalian transcriptome and the function of non-coding DNA sequences. *Genome Biol* 2004;**5**:105.
55. Li WH. *Molecular evolution*. Sunderland, MA: Sinauer Assoc Inc; 1997.
56. Mukhametov LM. Sleep in marine mammals. *Exp Brain Res* 1894;**8**(Suppl):227–38.
*57. Siegel JM, Manger PR, Nienhuis R, Fahringer HM, Pettigrew JD. The platypus has REM sleep. *Sleep Res* 1997;**26**:177.
58. Siegel JM. Phylogeny and the function of REM sleep. *Behav Brain Res* 1995;**69**:29–34.
59. Kimura M. *The neutral theory of molecular evolution*. Cambridge: Cambridge University Press; 1983.
60. Krueger JM, Obal Jr F, Fang J. Why we sleep: a theoretical view of sleep function. *Sleep Med Rev* 1999;**3**:119–29.
61. Ruckebusch Y. The relevance of drowsiness in the circadian cycle of farm animals. *Anim Behav* 1972;**20**: 637–43.
62. Van Twyver H, Allison T. A polygraphic and behavioral study of sleep in the pigeon (*Columba livia*). *Exp Neurol* 1972;**35**:138–53.
63. Zepelin H. Mammalian sleep. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 3rd ed. Philadelphia: WB Saunders Co; 2000.
64. Voss U. Functions of sleep architecture and the concept of protective fields. *Rev Neurosci* 2004;**15**:33–46.
65. Calder WA. Scaling energetics of homeothermic vertebrates: an operational allometry. *Annu Rev Physiol* 1987;**49**:107–20.
66. Bennington JH. Sleep homeostasis and the function of sleep. *Sleep* 2000;**23**:959–66.
67. Tobler I. Phylogeny of sleep regulation. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 3rd ed. Philadelphia: WB Saunders; 2000.
68. Noakes TD, St Clair Gibson A, Lambert EV. From catastrophe to complexity: a novel model of integrative central neural regulation of effort and fatigue during exercise in humans. *Br J Sports* 2004;**38**:511–4.
69. Gamundí A, Bernácer R, Roca C, Nicolau MC, Rial RV. Behavioral sleep in the lizard *Gallotia galloti*. *J Sleep Res* 1998(Suppl 2):7.
*70. Rose B. Factors affecting activity in *Sceloporus virgatus*. *Ecology* 1981;**62**:706–16.
71. Tobler I, Borbely A. Sleep and the EEG spectra in the pigeon (*Columba livia*) under baseline and after sleep deprivation. *J Comp Physiol* 1988;**163**:729–38.
72. Oishi T, Ohashi K. Effects of wavelengths of light on the photoperiodic gonadal response of blinded-pinealectomized Japanese quail. *Zool Sci* 1994;**10**:757–62.
73. Foster RG, Hankins MW. Non-rod, non-cone photoreception in the vertebrates. *Prog Retin Eye Res* 2002;**21**:507–27.
74. Osol G, Schwartz B, Foss DC. Effect of time, photoperiod, and pinealectomy on ocular and plasma melatonin concentrations in the chick. *Gen Comp Endocrinol* 1985;**58**: 415–20.
75. Vakkuri O, Rintamaki H, Leppaluoto J. Presence of immunoreactive melatonin in different tissues of the pigeon (*Columba livia*). *Gen Comp Endocrinol* 1985;**58**:69–75.
76. Falcón J. Cellular circadian clocks in the pineal. *Prog Neurobiol* 1999;**58**:121–62.

77. Deguchi T. Rhodopsin-like photosensitivity of isolated chicken pineal gland. *Nature* 1981;**290**:706–7.
78. Yoshikawa T, Oishi T. Extraretinal photoreception and circadian systems in nonmammalian vertebrates. *Comp Biochem Physiol* 1998;**119**:65–72.
79. Crompton AW, Taylor CR, Jagger JA. Evolution of homeothermy in mammals. *Nature* 1978;**272**:333–6.
80. Mintz EM, Phillips NH, Berger RJ. Daytime melatonin infusions induce sleep in pigeons without altering subsequent amounts of nocturnal sleep. *Neurosci Lett* 1998; **258**:61–4.
81. Rial RV, Nicolau MC, López-García JA, Almirall H. On the evolution of waking and sleeping. *Comp Physiol Biochem* 1993;**104**:189–93.
*82. Nicolau MC, Akaârir M, Gamundí A, González J, Rial RV. Why we sleep: the evolutionary pathway to the mammalian sleep. *Prog Neurobiol* 2000;**62**:379–406.
83. Belekhova MG. Neurophysiology of the forebrain. In: Gans C, Northcutt RG, Ulinski P, editors. Biology of the Reptilia, vol. 10. London: Academic Press; 1979.
84. Aboitiz F, Montiel J, Morales D, Concha M. Evolutionary divergence of the reptilian and the mammalian brains: consideration on connectivity and development. *Brain Res Rev* 2002;**39**:141–53.
*85. Sjölander S. Some cognitive breakthroughs in the evolution of cognition and consciousness and their impact on the biology of language. *Evol Cogn* 1995;**1**:3–11.
86. Edelmann GM, Tononi G. *A universe of consciousness*. New York: Basic Books; 2000.
87. Edelman DB, Baars BJ, Seth AK. Identifying hallmarks of consciousness in non-mammalian species. *Conscious Cogn* 2005;**14**:169–87.
88. Ten Donkelaar HJ, Nieuvehuys R. The brainstem. In: Gans C, Northcutt RG, Ulinski P, editors. *Biology of the Reptilia*, vol. 10. New York: Academic Press; 1979. p. 133–200.
*89. Saper CS, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005;**437**:1257–63.
90. Kavanau JL. Evolutionary approaches to understanding sleep. *Sleep Med Rev* 2005;**9**:141–52.
91. Webb WB. Sleep as an adaptive response. *Percept Motor Skills* 1974;**38**:1023–7.
92. Meddis R. *The sleep instinct*. London: Routledge and Kegan Paul; 1974.

Sleep Medicine Reviews (2007) 11, 411–417

ELSEVIER

SLEEP MEDICINE reviews

www.elsevier.com/locate/smrv

REPLY TO INVITED COMMENTARY

Sleep and wakefulness, trivial and non-trivial: Which is which?

Rubén V. Rial*, María C. Nicolau, Antoni Gamundí, Mourad Akaârir, Sara Aparicio, Celia Garau, Silvia Tejada, Catalina Roca, Lluis Gené, David Moranta, Susana Esteban

Laboratori de Fisiologia, Institut Universitari de Ciències de la Salut, Universitat de les Illes Balears, 07122 Palma de Mallorca, Spain

Introduction

Our main interest in writing a review on the trivial nature of sleep[1] was asserting that the main function of sleep is merely adapting the activity of the organism to the light-dark cyclic changes of the planet but also to confront the triviality of sleep with the non-trivial functions of wakefulness. We are happy to see that our viewpoint has provoked a discussion on many aspects of sleep which in our opinion are taken for granted but actually lack sufficient objective support. We are thus grateful to Rattenborg and co-workers[2] for having accepted the invitation to criticize our review. We examine next these criticisms.

The regulation of rest in poikilotherms

In our review, we proposed that the evidence for rest regulation in poikilothermic animals is insufficient and far from conclusive. On the contrary, there is an overwhelming amount of data showing that poikilotherms could persist resting immobile during long periods. For instance, every amateur herpetologist knows that frogs, turtles, snakes and lizards can spend weeks and even months in almost total inactivity, without signs of discomfort and without harmful effects. This means that their rest is not regulated and what is really important is their activity time. The discrepancy between these widely known facts and the experimental data obtained in several sleep laboratories should be due to mistakes introduced either in the design or in the interpretation of the results. In our opinion, a part of the problem lies in ignoring the effects not only of fatigue, which at least in humans has been found to be independent of sleepiness,[3] but also of stress. We believe that sleep deprivation without stress contamination has been produced, if any, in a very limited number of cases. However, experiments in poikilothermic animals could have been flawed in a number of additional ways. For instance, certain experiments in *Drosophila*[4] observed, that periods of immobility greater than 5 min resulted in decreased responsiveness to mechanical stimulation. This was interpreted as sleep-provoked raised thresholds. However, this result is different from others[5,6] which found that the *Drosophila* responsiveness to most sensory systems is inversely related to the overall level of arousal. Nevertheless, insects suffer activity-related variations in body temperature[7] even in a constant temperature environment.[8] Thus, regarding the counterproofs argued by Rattenborg and

*Corresponding author.
E-mail address: rvrial@uib.es (R.V. Rial).

1087-0792/$ - see front matter
doi:10.1016/j.smrv.2007.06.001

co-workers, the results of sleep deprivation in insects could have been due, not only to stress, but also to activity-related temperature changes, which would modify first the sensory thresholds and also the activity levels later. Similar concerns are raised by experiments performed in honeybees[9] in which forced activity caused a rebound of increased rest, seemingly independent of fatigue. However, earlier experiments[10,11] also found that, as we already described for *Drosophila*, the sensory sensitivity in honeybees was maximal during dark time. In conclusion, *Drosophilas* and honeybees could be resting but quite awake during nocturnal rest.

Regarding the studies performed on knock-out *per*^{01} flies,[4] Rattenborg and co-workers state that a consequence of our hypothesis is that insects lacking circadian rhythms should not rest. This is a naïve simplification that we would never dare to propose. Turning to mammals, the destruction of the suprachiasmatic nucleus, which can be considered in some way similar to the *per*^{01} inactivation, leads to a de-synchronization[12] entirely similar to that observed in knock-out animals but never causes the disappearance of rest and activity alternations. That is, vertebrates and invertebrates have indeed circadian clocks of rest–activity cycles, but they also have additional controls for suppression of motor output, for increasing (or perhaps decreasing) sensory thresholds, to select resting places, body positions and so on.

However, instead of lengthening this discussion with the pros and the cons of every experiment seemingly opposed to our viewpoint, we will rather take a panoramic look on the evolution of rest/sleep in the entire animal kingdom. Most probably, the main living animal groups stem from antecessors already present in the Precambrian Ediacaran fauna, which flourished ~570 million years ago. The common antecessors of insects and vertebrates thus began diverging until reaching the morphology and physiology that we observe nowadays. This immense time span could explain that the anatomic and functional differences between two insect orders, for instance, *Diptera* (flies) and *Hymenoptera* (honeybees) could be higher than within the whole mammalian class.[13] It is surprising, however, that amongst this huge animal diversity, the main neurotransmitter systems, serotonin, dopamine, epinefrine, norepinefrine, histamine, and acetylcholine, including their synthesizing pathways and receptors, are evolutionarily conserved and involved in similar functions: emotion, sensitivity, reinforcement but also rest/sleep.[14–16] Amongst these substances, melatonin, the clock and calendar molecule, is perhaps the most universally conserved substance, in terms of constant structure and function.[17] This clearly shows the importance of light/dark cycles in live beings. Currently, we are beginning to have a rough understanding of the complexity of the factors involved in the control of the circadian cycles of activity and rest and the variations in their anatomical, biochemical and physiological details. However, in order to understand the meaning of the similarities and differences, we should be able to distinguish between homology and analogy for every detail. We are far from being able to make such fine distinction and, as an example, we do not reach an agreement on the analogies and homologies between the rest/sleep of mammals and reptiles.[18–20] If it is hard to reconcile the different viewpoints in this minor aspect of the evolution of sleep, the task to identify homologies and analogies in the rest/sleep of insects and mammals should be even harder. Therefore, we end the present discussion remarking the differences described in previous paragraphs to counterpoint the similarities indicated by Rattenborg and co-workers. Additionally, some traps arising when comparing simple animals with mammals have been pointed out by Hendricks et al.[21] For instance, if one focuses on the capabilities exclusive of the mammalian brain, a fish, a sea slug or an insect have little to contribute, as some features of sleep that have intrigued the researchers do not appear in simple animals. These traits are so different or so difficult to identify that the effort to study them might not be justified in the present state of knowledge. Describing in detail the neuroanatomy and neurophysiology of rest mechanisms in fruitflies or *Aplysia* may be such endeavour. It should be remarked that these cautions have been proposed by researchers who openly defend the use of simple animals to understand sleep.[21]

The homeostatic regulation of sleep in mammals

We find that many sleep deprivation experiments, designed to prove homeostasis, are seriously contaminated by fatigue, stress, learned helplessness impairments, or conflicts between opposite needs of being simultaneously active and inactive. In spite of this, we also find quite compelling the homeostasis after the experiments of sleep extension.[22] After granting the homeostasis, the next question is what sleep does regulate. Sadly, apart from the trivial answer, i.e., to warrant rest, nobody knows another one. Rattenborg and co-workers assign a high value to the SW EEG as it is considered the best

indicator of the homeostatic sleep pressure[23] and pose several questions on the SW rebound observed after sleep deprivation and on the localized SW rebound observed after local exercise or learning. However, it is likely that Rattenborg and co-workers will agree in recognizing that the SW EEG is not a physiological variable; it must be an epiphenomenon of another truly valuable physiological process. Looking for such benefit, we can choose between the memory consolidation hypothesis, the alternative preferred by Rattenborg and co-workers, or the trivial, rest-providing hypothesis defended in our review. However, we believe that nobody would dare to negate the direct effect of sleep in providing rest. Therefore, the difference between the two hypotheses is that one of them asks for more: sleep provides rest, but also should provide an additional advantage. Therefore the second hypothesis is onerous. We will discuss the empirical problems of the memory consolidation hypothesis in later sections and we return to the SW rebounds. We know that the SW EEG power is related to increased brain adenosine levels[24] which reflect in turn the cellular energy charge and proceed from the degradation of ATP, AMPc and from the hepatic synthesis of purine rings.[25] Could these processes be a requisite for memory consolidation, or do they simply reflect an increased use? In our opinion, the last alternative has, by large, a much higher amount of empirical evidence. But even if we ignore such evidence, the simplest alternative should be accepted by default. Being asleep is always equivalent to be resting and in absence of strong evidence, no supplementary function should be requested. This drives us to the next question: is sleep necessary for memory processing?

Sleep and memory processing

Several recent studies suggest that sleep in many species may be involved in memory processing and neural plasticity. However, the evidence is far from conclusive. This is perhaps recognized by the word "suggest" and "may" used by Rattenborg and co-workers. The memory consolidation hypothesis has been now extended with genomic studies, a topic to which Rattenborg and co-workers give a high importance. However, even early reports already observed that the important "plasticity-related" genes are more highly expressed in rats' wakefulness than in sleep.[26–29] In another report, studying ~10 000 genes,[30] only 0.5% was differentially expressed across behavioural states, but it was emphasized that those showing greater expression in waking than sleep constituted the most important functional categories. This finding confirms the obvious result that the brain is exceedingly more active during wakefulness than during sleep, agreeing with what we propose: sleep is trivial when compared with waking. "*But why does sleep need a 'clear biological function' at all? It is being awake that needs an explanation, and presumably its explanation is obvious. Animals—unlike plants—need to be awake at least part of the time in order to search for food and procreate*". These words, from Dennet,[31] received full confirmation from genomic studies: "*many of the genes upregulated during wakefulness and sleep deprivation relative to sleep are involved in neural plasticity, suggesting that plasticity changes, inasmuch as they require the induction of genes, occur during wakefulness, rather than during sleep*".[28]

Rattenborg and co-workers provide references to several reviews defending the real existence of a relation between sleep and memory consolidation and also to a lower number of reviews opposing it. We would like to add two more of the latter.[32,33] Specially, Vertes[33] makes a demolishing attack to the hypothesis. However, the main arguments against the hypothesis were already specified in our review.[1] We think that they are strong enough, but we will not insist on them here. Instead, remarking the intensity of the debate already contradicts the conclusion reached by Rattenborg and coworkers. An impartial reader would not see "clarity" at all in this subject and we do not feel that the contradictory evidence for sleep-dependence memory processing and plasticity, be in insects, be in vertebrates, poses a significant challenge to our hypotheses.

Vulnerability during sleep

The supposed vulnerability of animals during sleep is another undemonstrated statement of Rattenborg and co-workers, as it is well known that victims of predation are the very young, the sick and the old, even when they are wide awake. This is consistent with the fact that many prey animals, i.e., rodents, sleep over 12 h per day, which is much more than many predators.[34] Nevertheless, in a review[35] signed by several of the authors arguing our review, it is recognized that predators and preys have coevolved, mutually adjusting their behaviour. This is reflected in the plasticity of sleep, in the sense that animals trade off sleep for security, a tenet with which we heartily agree. However, we do not understand why Lima et al.[35] do not continue recognizing the immediate

consequence: most sleep traits, but also the whole sleep is optional. Some animals can do without REM, others spend most inactive time in drowsiness, which is an incomplete form of sleep, others sleep with only an eye and half a brain and even some can suppress completely the sleep during long periods, all without harm. That is, animals only sleep when they have nothing else to do. Moreover, while these animals can survive the lack of sleep, they continue to rest and to keep strong rest/activity cycles. Contrary to the affirmation of Rattenborg et al., dolphins do not have continuous activity. Instead, they have strong activity–rest cycles with a peak between 12 and 16 h and a trough between 0 and 3 h, with abundant bottom-rest and surface-rest periods.[36] Similarly, birds show unequivocal rest during their asymmetric vigilance, and the herbivores' drowsiness could also be considered as a form of wakefulness accompanied by motor rest. Therefore, rest/activity cycles are maintained even in absence of full sleep behaviour, that is, opposite to sleep, animals do not trade off rest with security. We are aware that some animals can shift the timing of their activity–rest periods,[37] but this does not contradict our position; while we know animals without sleep, or with greatly reduced/modified sleep, no animal exists without rest–activity alternations. Sleep enforces such alternations, but they are preserved even in absence of sleep. Thus, the reasoning of Lima et al.[35] should be reversed: animals are not vulnerable when they sleep; instead, they avoid sleep when vulnerable and only enter in full sleep when the risk of predation is low.

Natural selection, parsimony and falsability

Rattenborg and co-workers consider that natural selection could act indirectly on REM sleep through its interrelationships with performance during wakefulness. We have already discussed some aspects of the sleep memory consolidation hypothesis and we would perhaps agree with Rattenborg and co-workers if the memory consolidation could have been undisputedly demonstrated. Nonetheless, we can add: if Mother Nature had modified the amount of REM to benefit a waking trait, it should have acted directly on waking instead of taking a tortuous path, from waking to NREM, to finally reach REM where the memory consolidation allegedly occurs. The defenders of the memory consolidation hypothesis answer this problem by the establishment of a second, yet empirically false, hypothesis: consolidation is impossible during active time. In summary, the proposition is disputable in experimental terms, non-parsimonious and false in logical consequences. It is perhaps even unfalsable: if memory consolidation cannot occur without sleep and if animals cannot live without sleep, no animal exists on which an experiment could be performed to falsify the hypothesis.

Phylogenetic correlations of sleep

Rattenborg and co-workers affirm that we incorrectly cite a lack of phylogenetic correlation with the amount of sleep, obviating thus a recent review.[38] However, we have many concerns on this review. First of all, the title of the review refers to "*A phylogenetic analysis…*" and in the methods section the authors carefully explain how the phylogenetic analysis was performed. However, we see a phylogenetic conclusion nowhere else apart from the first sentence of the discussion. The review ends concluding that body mass is not directly related to sleep structure, that species with high basal metabolic rate (BMR) engage in less SWS, that large brained animals have more REM, that those at higher predation risk have less REM and that precocial animals have more REM. Where are the phylogenetic relationships? To our knowledge, none of the mentioned variables have a relationship with phylogeny. We would have been happier if some of their conclusions were different. For instance, the statement that "*the positive relationship between* (*relative*) *brain mass and %REM sleep* suggest *that* mammals *with relatively greater encephalization allocate more time asleep to REM*"[38] (our emphasis), would have greatly improved if the word "suggest" had been changed to "demonstrates" (however, this is the word actually, and *wrongly,* used by Rattenborg and co-workers[2] when quoting the report[38]). Also, writing "primates" (for instance) instead of "mammals" would have effectively substantiated a phylogenetic aspect. Sadly, it seems that the results obtained did not allow for such modified redaction. We feel therefore that our affirmation on the absence of correlation between phylogeny and REM sleep can be maintained.

Pursuing with the absence of a significant correlation between sleep and phylogeny, Noser et al.[39] explain that sleep has been investigated in 17 primate species showing: (i) that sleep stages as well as the composition of sleep cycles are similar to those of humans and (ii) inter-species differences have been found, with low amounts of deep sleep in species with intense nocturnal predation pressure (references therein). We are glad to see

that this study confirms one of the conclusions of Lesku et al.[38] On the other hand we regret the absence of relation between encephalization and sleep in an analysis performed within a single phylogenetic branch and we feel compelled to believe that such relationship does not exist. Meanwhile, we wonder on the value of a "phylogenetic" study in which the conclusions "*found support for some hypothesis for the* function *of sleep, such as facilitating memory consolidation or learning*"[38] if the alleged phylogenetic relationship does not hold for primates.

The metaphor of non-coding DNA

Rattenborg and co-workers consider that our metaphor relating non-coding DNA and sleep, in fact, argues against our main thesis because one would not expect constancy in the characteristics of sleep if sleep did have no adaptive value. Retorting the argument, we consider that sleep has, in fact, a rather high variability. We already mentioned[1] that the variation in REM ranges from 0% to 60% in different animals, and also that animals exist with long and short sleep, even without any sleep at all. We can add animals with unihemispheric and bihemispheric sleep, with REM sleep accompanied with low voltage mixed frequency EEG, but also with slow wave REM EEG. How much variation is acceptable to go on thinking that sleep is homogeneous? Is there a valid rule to affirm homogeneity? We think that sleep shows a rather high plasticity, to use the same word of Lima et al.[35] and such large variability as well as the inextricable complexity of sleep gives full support to the metaphor.

Evolution and adaptation

Perhaps we can agree with Rattenborg and co-workers in one aspect: accepting adaptation as a last resort is contrary to current practice in the study of animal behaviour (we would add: this is particularly true in sleep scholars). However, we think that democracy is unrelated to the quest for scientific truth. We agree with Rattenborg and co-workers that erecting hypotheses is an absolute need for science, but we claim that not all competing hypothesis should be tested against observations. Adaptations can be invented too easily. For instance, a hypothesis proposing the existence of premonitory dreams would be very attractive and would have some democratic merits. However, to give scientific value to such hypothesis, *a firm and positive proof should be demanded to those defending the existence of premonitory dreams. On the other hand, no proof should be asked to those negating their existence* (in fact, a proof of non-existence is, by pure logic, impossible). Now, if we change two words in the emphasized sentence and place "*memory consolidation*" instead of "*premonitory dreams*" the amount of logic contained in it will remain constant. Please note that we are not comparing premonitory dreams with memory consolidation; what we mean is that the need of a *strict and positive proof* is the same for every non-parsimonious hypothesis. This is the principle used to exclude, not only magic thinking and superstition, but also hypotheses without a firm experimental support. On the contrary, the absence of adaptive value for sleep should be never forced to observational contrast.

Conclusion

Rattenborg and co-workers end their comment stating that they find little support for the ideas or evolutionary arguments set forth in our review. However, they only have argued against some of our proposals. For instance, they put forward no objection against our affirmation that most experiments on sleep deprivation are, in fact, experiments on conflict between simultaneous drives to remain inactive and active and therefore such experiments give little evidence on the function of sleep. The probable helplessness state achieved as a result of the deprivation procedures is neither objected.[1] Therefore we can assume that they agree with us in these aspects. However, if it is so, they should not have used arguments based on sleep deprivation experiments. This contradiction, in fact, should invalidate their support, for instance, to the memory and learning consolidation hypothesis, to the existence of homeostatic regulation of sleep in poikilotherms or to the attribution to sleep of many other traits, which have been obtained through sleep deprivation. Indeed, we would not consider their dialectic flaw as a proof against such hypotheses. Instead we prefer to consider it as a proof of the existence of researchers who uncritically support undemonstrated hypothesis. We propose that the triviality of sleep is awesome when compared with the undisputable importance of waking. We also propose that the evolution allowed the appearance of animals with conscious wakefulness thanks to the cortical development. As a result, sleep appeared as a "spandrel"[40] in the evolution of conscious waking. It should be noted that this hypothesis continues

being parsimonious, because it does not need to add anything to several undisputedly mammalian observational facts which up to now have not been considered to account for the evolution of vigilance: the cortical development, the simultaneous appearance of consciousness and even the existence of new neurophysiological signs such as the cortical arousal EEG reaction as well as the mixed frequency, low amplitude EEG typical of mammalian waking.[41] In front of this waking centred paradigm, Rattenborg and co-workers have proposed that the cortical development allowed the production of SWS,[5,7] a state whose function is, at most, a beautiful but unproven guess. There is no need to insist on the low value of the observational and epistemological support of their proposal.

Acknowledgements

This work has been performed thanks to a grant from the Ministerio de Ciencia y Tecnología of the Spanish Government number BFI2002-04583-C02-02.

References

1. Rial RV, Nicolau MC, Gamundi A, Akaârir M, Aparicio S, Garau C, et al. The trivial function of sleep. *Sleep Med Rev* 2007; **11**:311–25.
2. Rattenborg NC, Lesku JA, Martinez-Gonzalez D, Lima SL. The non-trivial functions of sleep. *Sleep Med Rev* 2007; **11**:405–9.
3. Merkelbach S, Schulz H. What have fatigue and sleepiness have in common?. *J Sleep Res* 2006;**15**:105–6.
4. Shaw PJ, Cirelli C, Greenspan RJ, Tononi G. Correlates of sleep and waking in *Drosophila melanogaster. Science* 2000; **287**:1834–7.
5. Krishnan B, Dryer SE, Hardin PE. Circadian rhythms in olfactory responses of *Drosophila melanogaster. Nature* 1999;**400**:375–8.
6. Krishnan B, Levine SE, Lynch MK, Dowse HB, Funes P, Hall JC, et al. A new role for cryptochrome in a Drosophila circadian oscillator. *Nature* 2000;**411**:313–7.
7. Heinrich B. *Insect thermoregulation*. New York: Wiley; 1981.
8. Lehmann FO. Ambient temperature affects free-flight performance in the fruit fly *Drosophila melanogaster. J Comp Physiol B* 1999;**169**:165–71.
9. Sauer S, Herrmann E, Kaiser W. Sleep deprivation in honey bees. *J Sleep Res* 2004;**13**:145–52.
10. Kayser W, Steiner-Kaiser J. Neuronal correlates of sleep, wakefulness and arousal in a diurnal insect. *Nature* 1983; **301**:707–9.
11. Chen DM, Christianson JS, Sapp RJ, Stark WS. Visual receptor cycle in normal period mutant drosophila: microespectrophotometry, electrophysiology, and structural morphometry. *Vis Neurosci* 1992;**9**:125–35.
12. Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc Natl Acad Sci USA* 1972;**69**:1583–6.
13. Wilson E. *The diversity of life*. Cambridge, MA: Harvard University; 1992.
14. Nassel DR, Elekes K. Aminergic neurons in the brain of blowflies and Drosophila: dopamine- and tyrosine hydroxilase-immunoreactive neurons and their relationships with putative histaminergic neurons. *Cell Tissue Res* 1992;**276**: 147–67.
15. Peroutka SJ, Howell TA. The molecular evolution of G protein-coupled receptors: focus on 5-hydroxitryptamine receptors. *Neurpharmacol* 1994;**33**:319–24.
16. Pani L, Gessa GL. Evolution of the dopaminergic system and its relationships with the psychopathology of pleasure. *Int J Clin Pharmacol Res* 1997;**17**(2–3):55–8.
17. Hardeland R. The presence and function of melatonin and structurally related indoleamines in a dinoflagelate, and a hypothesis on the evolutionary significance of these tryptophan metabolites in unicellulars. *Experientia* 1993;**49**:614–22.
18. Rattenborg NC. Evolution of slow-wave sleep and palliopallial connectivity in mammals and birds: a hypothesis. *Brain Res Bull* 2006;**69**:20–9.
19. Rial RV, Nicolau MC, Gamundi A, Akaârir M, Garau C, Aparicio S, et al. Comments on evolution of sleep and the palliopallial connectivity in mammals and birds. *Brain Res Bull* 2007; in press.
20. Rattenborg NC. Response to commentary on evolution of slow-wave sleep and palliopallial connectivity in mammals and birds: a hypothesis. *Brain Res Bull* 2007; in press.
21. Hendricks JC, Sehgal A, Pack AI. The need for a simple animal model to understand sleep. *Progr Neurobiol* 2000; **61**:339–51.
22. Achermann P, Dijk DJ, Brunner DP, Borbély AA. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. *Brain Res Bull* 1993;**31**:97–103.
23. Tobler I. Phylogeny of sleep regulation. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 77–90.
24. Benington JH, Kodali SK, Heller HC. Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. *Brain Res* 1995;**692**:79–85.
25. Chagoya de Sánchez V, Hernández-Muñoz R, Sanchez L, Vidrio S, Yañez L, Suarez J. Circadian variations of adenosine levels in blood and liver and its possible physiological significance. *Life Sci* 1983;**33**:1057–64.
26. Cirelli C, Pompeiano M, Tononi G. Neuronal gene expression in the waking state: a role fro the locus coeruleus. *Science* 1996;**274**:1211–5.
27. Cirelli C, Tononi G. Differences in gene expression between sleep and waking as revealed by mRNA differential display. *Mol Brain Res* 1998;**56**:293–305.
28. Cirelli C, Tononi G. Differential expression of plasticity-related genes in waking and sleep and their regulation by the monoaminergic system. *J Neurosci* 2000;**20**:9187–94.
29. Tononi G, Cirelli C. Modulation of brain gene expression during sleep and wakefulness: a review of recent findings. *Neuropshychopharmacol* 2001;**5**:S28–35.
30. Cirelli C, Tononi G. Gene expression in the brain across the sleep-waking cycle. *Brain Res* 2000;**885**:303–21.
31. Dennet DC. *Darwin's dangerous idea*. London: Penguin Books; 1995.
32. Vertes RP, Eastman KE. The case against memory consolidation in REM sleep. *Behav Brain Sci* 2000;**23**:1057–63.
33. Vertes RP. Memory consolidation in sleep: dream or reality. *Neuron* 2004;**1**:135–48.
34. Campbell SS, Tobler I. Animal sleep: a review of sleep duration across phylogeny. *Neurosci Biobehav Rev* 1984; **8**:269–300.

35. Lima SL, Rattenborg NC, Lesku JA, Amlaner CJ. Sleeping under the risk of predation. *Anim Behav* 2005;**70**:723–36.
36. Sekiguchi Y, Kohsima S. Resting behavior of captive dolphins *Tursiops truncata*. *Physiol Behav* 2003;**79**:643–53.
37. Fenn MGP, Macdonald DW. Use of middens by red foxes: risk reverses rhythms of rats. *J Mammal* 1995;**76**:130–6.
38. Lesku JA, Roth II TC, Amlaner CJ, Lima SL. A phylogenetic analysis of sleep architecture in mammals: the integration of anatomy, physiology, and ecology. *Am Nat* 2006;**168**:441–53.
39. Noser R, Gygax L, Tobler I. Sleep and social status in captive gelada baboons (*Theriopitecus gelada*). *Behav Brain Res* 2003;**147**:9–15.
40. Gould SJ, Levontin RC. The spandrels of San Marco and the panglosian paradigm: a critique of the adaptationist programme. *Proc R Soc London (B)* 1979;**205**:581–98.
41. Nicolau MC, Akaârir M, Gamundí A, González J, Rial RV. Why we sleep: the evolutionary pathway to the mammalian sleep. *Prog Neurobiol* 2000;**62**:379–406.