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Review

The Two-Process Model: Origin of Its Concepts and Their Implications

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Abstract: The two-process model of sleep regulation has served as a conceptual framework in the last four decades for understanding sleep physiology. In the 1970s, long-term recordings of sleep in rats were obtained thanks to EEG telemetry. NonREM sleep and REM sleep were found to differ in their time course and response to light-dark protocols. There were indications for their coupling to the circadian system, in particular the light-dark and the dark-light transitions. With the advent of quantitative EEG analysis, slow-wave activity in nonREM sleep was recognized as a sleep-wake-dependent variable. The term "sleep homeostasis" was coined to specify the regulated balance between sleep and waking. The regulatory homeostatic process was designated as "Process S". In the two-process model, its interaction with the circadian pacemaker "Process C" can account for sleep duration under various experimental protocols. Local, use-dependent slow-wave activity changes were demonstrated in both humans and rats by the selective, unilateral activation of a cortical region prior to sleep. Finding that rest in invertebrates has sleep-like regulatory properties opened a new realm of animal studies. Comparative sleep studies in a broad variety of animal species confirmed the validity of the basic concepts of the two-process model. Recent studies have addressed sleep-related changes of brain temperature as an indicator of brain metabolism; the application of the model to Drosophila; the divergence of cortical and subcortical states; and sleep in an increasing number of species and taxa.

Keywords: two-process model; EEG analysis; sleep homeostasis; circadian rhythm; local sleep; comparative sleep studies

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1. Introduction

The two-process model of sleep regulation was first described in the early 1980s and has since then served as a useful conceptual framework in sleep research. The origins of the model were recently retraced [1]. It has been subjected to reappraisal by the authors involved in its development [2]. Here, we highlight the origin of the concepts underlying the model and discuss some implications.

2. Circadian Rhythms

Recording rest-activity cycles has been the major approach to exploring circadian rhythms in rodents. In their seminal paper, Pittendrigh and Daan [3] proposed that the circadian rest-activity rhythm is governed by two mutually interacting oscillators that are coupled separately to sunrise (M) and sunset (E). The authors dubbed this pacemaker structure "a clock for all seasons" because it could discriminate daylength and hence adjust to seasonal changes of the photoperiod.

The development of a miniature telemetry system and the use of a laboratory computer (Figure 1) were important because they allowed us to obtain long-term recordings of sleep in unrestrained rodents. In the 1970s, we used light as an experimental variable to explore its effect on sleep in relation to the circadian phase. By applying short light-dark (LD) cycle protocols, we showed a D-induced enhancement of REM sleep that was largest

in the circadian rest period, whereas the L-induced enhancement of nonREM sleep was maximal in the circadian activity period [4]. These observations led us to explore the time-course of the two sleep states in different lighting protocols: during a gradual shortening of the photoperiod [5], during continuous darkness or continuous light, and during a skeleton photoperiod [6]. We concluded that the E-M two-oscillator hypothesis may also apply to sleep, nonREM sleep being coupled to the DL-transition and REM sleep to the LD-transition.

Figure 1. The authors in front of the PDP-11 computer in mid 1980s. It served for data logging of long-term experiments and for analysis of the sleep EEG.

We did not pursue this approach further because the analysis of the sleep EEG revealed a facet of sleep regulation which could be investigated by sleep deprivation rather than by light.

3. Recovery Process

Berger and Oswald [7] were the first to report an increase of slow-wave sleep after sleep deprivation in human subjects. Feinberg's group [8], using period-amplitude analysis of the EEG, showed that during baseline sleep, delta activity shifted towards lower frequencies and declined in amplitude. They speculated that the changes may reflect the kinetics of metabolic processes underlying sleep and may be related to the "goodness of sleep". By applying period-amplitude analysis of the EEG in rats, we showed that the low-frequency fraction of nonREM sleep (SWS) declined over the course of a 12 h light period [9]. An additional important observation was that SWS was enhanced during recovery sleep after sleep deprivation and that this effect depended on the duration of prior wakefulness. This led to the proposition that SWS represents an intensity parameter of nonREM sleep and that its decline during sleep reflects a recovery process. In a preliminary version of the two-process model, the recovery process and the circadian system were considered to be two separate facets of sleep regulation [10]. We and Mistlberger showed that the circadian rhythm was not a prerequisite for the recovery process in nonREM sleep because the latter persisted in animals in which the circadian pacemaker in the suprachiasmatic nuclei had been lesioned [11,12].

4. Sleep Homeostasis

The term "sleep homeostasis" was first proposed in a book chapter on functional aspects of sleep [10]. It can be defined as a regulated balance between sleep and waking [13]. A subsequent article proposed that sleep homeostasis denotes the regulation of the sleep process relative to an internal reference level [14]. Slow waves were considered an indicator of sleep intensity that could reflect a restitutional function of sleep.

The term sleep homeostasis has gained popularity and is widely used. For example, recent reviews refer to the rising homeostatic sleep pressure during waking leading to a compensatory sleep rebound or recovery sleep, strengthening the idea that it reflects some important restorative process [15,16].

5. Process S

In the two-process model, Process S is designated as a regulatory process that is determined by preceding sleep and wakefulness [17]. Its time course was derived from EEG slow-wave activity, an electrophysiological variable that declines during the daily sleep period in humans [18] and rodents [9]. The time course of its rise during the daily waking period was derived from slow-wave activity during multiple naps in humans [19] and from interspersed sleep episodes in rats [9].

The term "process" in Process S is meant to indicate a regulatory homeostatic principle that can be operationalized by an EEG correlate. It has given rise to several hypotheses concerning the underlying neural mechanisms. One of the best known propositions is the synaptic homeostasis hypothesis [20,21]. The authors posit that neuronal circuits increase in synaptic strength during waking and weaken during sleep. Some have used the term "homeostat", implying that it could be specified and localized. However, it is likely that all parts of the sleep circuitry in the brain can implement homeostasis [15] and even that factors from skeletal muscle may be involved [22]. Therefore, in view of our ignorance of the nature of sleep homeostasis, the general term "process" is still appropriate.

6. Interaction of S and C

Usually, the two processes S and C act in synergy and reinforce each other. By scheduling the recovery from sleep deprivation to the beginning of an animal's circadian activity period, a conflict is created. Its consequences were apparent in a 24 h sleep deprivation schedule that ended at the beginning of the animal's activity period [9]. A two-stage rebound of slow-wave sleep occurred, the second stage being delayed by 12 h from the light period. In the guinea pig, an animal with a weak circadian rest-activity rhythm [23], the sleep rebound was equal in the light and dark periods [24]. Forced desynchrony between the sleep-wake cycle and the circadian rhythm was applied to investigate the interaction between S and C in humans [25]. Sleep continuity was impaired when the enforced sleep period coincided with the circadian wake period.

In the two-process model, the duration of sleep is determined by the interaction of Process S with a threshold modulated by Process C [17]. In the extended version of the model, an upper threshold was added to define the duration of waking under free-running conditions [26]. The question of the type of continuous interaction of the two processes (linear or nonlinear) arose in conjunction with the forced desynchrony protocol [27]. While there are arguments for both types of interaction, the possibility of a nonlinearity in neurobehavioral metrics such as alertness and cognitive performance must also be considered.

7. NonREM-REM Sleep Cycle

The homeostatic part of the model was elaborated to include the ultradian nonREM-REM sleep cycle [28,29]. The initial buildup of slow-wave activity within a nonREM sleep episode was represented by the combined action of an exponentially increasing process and a saturation process. Based on a large set of empirical data, the model parameters were estimated and the performance tested on data from independent protocols [30]. A close fit was obtained between the empirical and simulated data.

8. Behavioral Homeostasis

Initially, EEG slow-wave activity served as the marker of sleep homeostasis. This led to the observation that its time course during sleep was comparable in humans and in rats. However, this approach was restricted to those animals in which the EEG could be

recorded. In invertebrates, the usual electrographic criteria are absent. The question arose of whether immobility periods have sleep-like properties. In other words, does rest deprivation induce a compensatory increase in resting behavior? To examine this possibility, cockroaches, Leucophaea maderae, were prevented from resting by manual rotation and slight shaking of their dish for 3 h [31]. In comparison to the control condition, immobility was enhanced in the first hour following rest deprivation. Additionally, in another cockroach strain, a 6 h rest deprivation gave rise to a compensatory response [32]. A similar effect was obtained in scorpions, another arthropod, following a 12 h rest deprivation by mechanical stimulation [33]. These were the first studies showing that rest in invertebrates shows a similar homeostatic regulation as sleep in homeotherms. The correspondence was confirmed in rats, where the time course of sleep continuity, indexed by a behavioral variable, the number of brief awakenings, and of EEG slow-wave activity was comparable for baseline conditions and sleep deprivation [34].

These early studies opened the sleep field to the realm of invertebrates and in particular to Drosophila as the prime organism for the genetic dissection of sleep [35,36]. Since then, the field has witnessed an explosive growth, and the number of citations of "sleep and Drosophila" has skyrocketed. Recent studies showed a sleep-like state that may be homeostatically regulated, even in animals without a centralized nervous system, such as Cassiopea [37] and Hydra vulgaris [38].

9. Local Sleep and Use Dependence

In his classical review chapter on the sleep-wake cycle, Moruzzi proposed that "sleep concerns primarily not the whole brain and not even the entire neocortex, but only those neurons or synapses, and possibly glia cells, which during wakefulness are responsible for, or related to, the brain functions concerned with conscious behavior." [39] (p. 121). He surmised that recovery in sleep depends on the type and intensity of activity during wakefulness and that neurochemical needs differ in different parts of the brain. He proposed that "sleep would permit a kind of local homeostasis". Moruzzi's ideas were taken up and extended by Krueger and Obál [40], who proposed a neuronal group theory of sleep in which synaptic plasticity plays a central role.

These theoretical considerations were clearly in need of empirical testing. To activate a region of the cortex selectively, we applied a prolonged vibratory stimulus to the contralateral hand prior to sleep [41]. This procedure was known to increase regional cerebral glucose metabolism and blood flow. Subsequent sleep showed a shift of EEG power in the low-frequency range towards the stimulated hemisphere. The change was limited to the central derivations situated over the somatosensory cortex and was restricted to the first hour of sleep. The result confirmed that activation of specific neuronal populations during wakefulness can cause regional changes during sleep that reflect an intensification of the sleep process. The experiment using eight EEG derivations did not allow for the precise localization of the use-dependent changes. Reto Huber, who joined Giulio Tononi's group, extended the results using a high-density EEG setup with 256 electrodes in a motor learning task [42].

This local, use-dependent facet of sleep was also investigated in rats, where the projection of the whiskers to the contralateral somatosensory cortex provided an ideal experimental model. The barrels in the cortex consist of a group of neurons receiving input from a single specific vibrissa. They are stimulated during exploratory behavior. After clipping whiskers unilaterally, recovery from sleep deprivation exhibited an interhemispheric shift of low-frequency power in nonREM sleep, which was contralateral to the side receiving input from the intact whiskers [43]. These results were reinforced by comparing the brain metabolism between the two sides [44]. In a subsequent study using a motor task, handedness was also shown to lead to EEG asymmetry during sleep [45]. Paw preference during food-reaching tasks led to changes over the contralateral cortex in the theta range during waking and in the delta range during subsequent sleep.

10. Comparative Sleep Studies

The comparison of sleep among different species provides information about its variation in nature and allows insights into general regulatory principles. Due to her background in zoology, Irene Tobler was particularly interested in this approach (Figure 2).

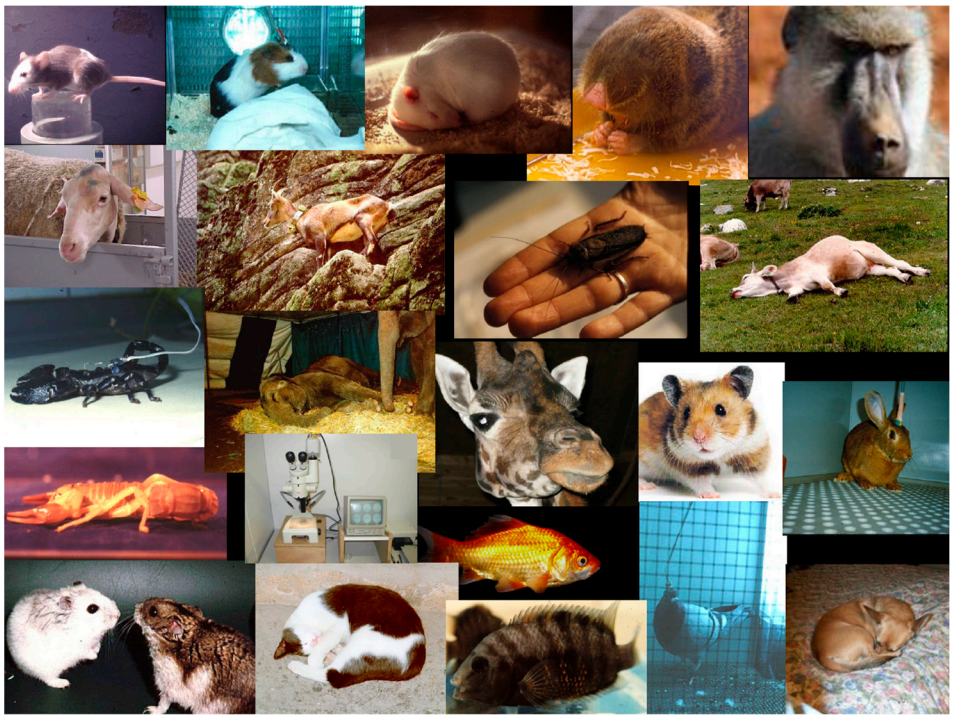

Figure 2. Composite picture of the animal species in which rest activity or sleep was analyzed by Irene Tobler.

Homeostasis of slow-wave activity that had been originally reported for rats was shown to also be present in diverse other rodent species: the Syrian hamster [46], the guinea pig [24], the Djungarian hamster [47], several mouse strains [48–50], and the blind mole rat, a fossorial animal [51]. In these studies, Tom Deboer and Vlad Vyazovskiy played a major role. Blind mole rats whose motor activity was recorded for several months showed a large intra- and inter-individual variability in their 24 h pattern [52]. In most animals, a free-running circadian rhythm was seen under continuous darkness. Despite the large ecological differences, their polysomnographic features were similar to those of other rodents.

Guinea pigs conformed to the predictions of the two-process model, but the low amplitude of the circadian rhythm caused equal effects of sleep deprivation in both the light and dark periods [23,24].

Cats studied in a light-dim cycle exhibited a low-amplitude circadian rhythm and responded with a rise in slow-wave activity to 14 h sleep deprivation [53]. Rabbits kept under light-dim conditions slept more in the light period, where they showed a declining trend of slow-wave activity in nonREM sleep [54]. Twenty-four hour sleep deprivation beginning at light onset caused an increase of slow-wave activity during recovery sleep.

In dogs, a behavioral index was used to study sleep homeostasis. Motor activity was measured continuously with an actometer worn on the collar [55]. Twenty-four hour sleep deprivation was followed by reduced motor activity and an increase in the number of low-activity episodes.

In perch and goldfish, light-induced activation was used to prevent the animals from having resting behavior for 6 or 12 h [56]. The interventions were followed by a

prolongation of rest periods and an increase of low-activity states, evidence of homeostatic regulation.

In animals in which homeostatic challenges were not possible, observational studies focused on the daily time course of rest activity, sleep, its behavioral characteristics, and seasonal changes. Studies were carried out on ibex in the wild [57], elephants in captivity [58] and giraffes kept in a zoological garden [59].

11. Perspectives

The homeostatic regulation of sleep indicates that it is an essential state or process. In his 1932 paper on the autonomic nervous system, Hess [60] considered that exploration at the level of tissues is important for comprehending the nature of sleep. He wrote, "The special mechanisms which bring about repair during sleep are hidden in the tissue. They have not yet been fully explained; their existence is only deduced from their effects; yet they lie at the heart of the problem of sleep, and the resting of the sense-organs, muscles, and psychic functions are only accessory factors facilitating restoration within the tissues". This line of reasoning corresponds to the arguments in a recent review on the "inescapable drive to sleep" [15] where the authors suggest that "the requirements for sleep could originate at the cellular level with neurons fatiguing with time spent awake, analogous to the metabolic fatigue of skeletal muscle with exercise". In fact, there is evidence that critical components of sleep regulation could reside in skeletal muscle [22]. Frank and Wisden propose that sleep may provide some fundamental "housekeeping" or metabolic function and that the decline of cortical temperature during nonREM sleep could be crucial for a restorative process. Brain temperature is a fundamental physiological variable that affects a variety of neural processes. Its homeostatic and circadian components have been analyzed by Paul Franken [61]. In the Franken lab, Sela et al. [62] demonstrated that the sleep-wake state sequence predicts temperature dynamics on a time scale of hours as well as in the order of seconds. This work is not only an outstanding example of the power of modeling but confirms the close relationship between the sleep-wake cycle and brain temperature.

Additionally, Adamantidis and de Lecea [63], addressing the temporal organization of hypothalamic homeostasis, highlight the large range of timescales involved in physiological and behavioral homeostatic processes. Imbalances and changes in internal states engender motivational drives and goal-directed behaviors. They intermesh with sleep homeostasis in a complex manner. The organization of responses to homeostatic challenges implicates neural networks beyond the hypothalamus. The question of whether sleep homeostasis and circadian rhythmicity are separate processes or are in multiple ways entangled was addressed by Franken and Dijk in their authoritative review [64].

The original, quantitative version of the two-process model allowed for a computer simulation of human sleep for various experimental protocols. The time constants of Process S and the amplitude and shape of Process C were derived from empirical data. An analogous approach was recently used for studying sleep in Drosophila [65]. The authors showed that the model provides empirically testable predictions regarding circadian and homeostatic control. The ultradian rhythm of sleep observed in loss-of-function mutants was predicted by a functional homeostatic process in the absence of the circadian pacemaker. The simulations showed a correlation between clock speed (period) and the rate of decay of sleep pressure, revealing a novel type of interaction between the two processes. Moreover, long sleep bouts were shown to be indicators of sleep intensity. Although the mathematics used in the simulations need further scrutiny [66], the power of Drosophila as a genetically tractable model of sleep regulation is reinforced by the simulation of the underlying processes within a theoretical framework.

The recognition of sleep as a local, use-dependent cerebral process has opened new avenues for research. It was shown that Process S can be derived from cortical firing rates alone, demonstrating that sleep homeostasis can be modelled at the local level [67]. Local sleep signs have been shown to occur in behaviorally awake animals [68]. A new type of divergence was recently reported for human sleep, where the neocortex and hip-

pocampus were in non-corresponding states, the hippocampus assuming a leading role in asynchronous state transitions [69]. A coexistence of sleep-like and wake-like EEG patterns was observed in different cortical areas [70]. These discrepancies indicate that the state definition is more complex than is generally assumed.

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References

1. Borbely, A. The two-process model of sleep regulation: Beginnings and outlook. *J. Sleep Res.* **2022**, *31*, e13598. [CrossRef] [PubMed]
2. Borbely, A.A.; Daan, S.; Wirz-Justice, A.; Deboer, T. The two-process model of sleep regulation: A reappraisal. *J. Sleep Res.* **2016**, *25*, 131–143. [CrossRef] [PubMed]
3. Pittendrigh, C.S.; Daan, S. Functional-analysis of circadian pacemakers in nocturnal rodents. 5. Pacemaker structure—Clock for all seasons. *J. Comp. Physiol.* **1976**, *106*, 333–355. [CrossRef]
4. Borbely, A.A.; Huston, J.P.; Waser, P.G. Control of sleep states in the rat by short light-dark cycles. *Brain Res.* **1975**, *95*, 89–101. [CrossRef] [PubMed]
5. Borbely, A.A.; Neuhaus, H.U. Daily pattern of sleep, motor-activity and feeding in rat—Effects of regular and gradually extended photoperiods. *J. Comp. Physiol.* **1978**, *124*, 1–14. [CrossRef]
6. Borbely, A.A.; Neuhaus, H.U. Circadian-rhythm of sleep and motor-activity in rat during skeleton photoperiod, continuous darkness and continuous light. *J. Comp. Physiol.* **1978**, *128*, 37–46. [CrossRef]
7. Berger, R.J.; Oswald, I. Effects of sleep deprivation on behaviour, subsequent sleep and dreaming. *J. Ment. Sci.* **1962**, *108*, 457–465. [CrossRef]
8. Church, M.W.; March, J.D.; Hibi, S.; Benson, K.; Cavness, C.; Feinberg, I. Changes in frequency and amplitude of delta activity during sleep. *Electroencephalogr. Clin. Neurophysiol.* **1975**, *39*, 1–7. [CrossRef]
9. Borbely, A.A.; Neuhaus, H.U. Sleep-deprivation—Effects on sleep and EEG in the rat. *J. Comp. Physiol.* **1979**, *133*, 71–87. [CrossRef]
10. Borbely, A.A. Sleep: Circadian rhythm versus recovery process. In *Functional States of the Brain: Their Determinants*; Koukkou, M., Lehmann, D., Angst, J., Eds.; Elsevier: Amsterdam, The Netherlands, 1980; pp. 151–161.
11. Tobler, I.; Borbely, A.A.; Groos, G. The effect of sleep-deprivation on sleep in rats with suprachiasmatic lesions. *Neurosci. Lett.* **1983**, *42*, 49–54. [CrossRef]
12. Mistlberger, R.E.; Bergmann, B.M.; Waldenar, W.; Rechtschaffen, A. Recovery sleep following sleep deprivation in intact and suprachiasmatic lesioined rats. *Sleep* **1983**, *6*, 217–233. [CrossRef]
13. Tobler, I.; Achermann, P. Sleep homeostasis. *Scholarpedia* **2007**, *2*, 2432. [CrossRef]
14. Borbély, A.A. The sleep process: Circadian and homeostatic aspects. In *Advances in Physiological Science*; Pergamon Press: London, UK, 1981; Volume 18, pp. 85–91.
15. Franks, N.P.; Wisden, W. The inescapable drive to sleep: Overlapping mechanisms of sleep and sedation. *Science* **2021**, *374*, 556–559. [CrossRef]
16. Nollet, M.; Franks, N.P.; Wisden, W. Understanding sleep regulation in normal and pathological conditions, and why it matters. *J. Huntingt. Dis.* **2023**, *12*, 105–119. [CrossRef]
17. Borbely, A.A. A two process model of sleep regulation. *Hum. Neurobiol.* **1982**, *1*, 195–204.
18. Borbely, A.A.; Baumann, F.; Brandeis, D.; Strauch, I.; Lehmann, D. Sleep-deprivation—Effect on sleep stages and EEG power-density in man. *Electroencephalogr. Clin. Neurophysiol.* **1981**, *51*, 483–493. [CrossRef]
19. Dijk, D.J.; Beersma, D.G.M.; Daan, S. EEG power density during nap sleep: Reflection of an hourglass measuring the duration of prior wakefulness. *J. Biol. Rhythm.* **1987**, *2*, 207–220. [CrossRef]
20. Tononi, G.; Cirelli, C. Sleep and synaptic homeostasis: A hypothesis. *Brain Res. Bull.* **2003**, *62*, 143–150. [CrossRef]
21. Tononi, G.; Cirelli, C. Steep function and synaptic homeostasis. *Sleep Med. Rev.* **2006**, *10*, 49–62. [CrossRef]
22. Ehlen, J.C.; Brager, A.J.; Baggs, J.; Pinckney, L.; Gray, C.L.; DeBruyne, J.P.; Esser, K.A.; Takahashi, J.S.; Paul, K.N. Bmal1 function in skeletal muscle regulates sleep. *Elife* **2017**, *6*, e26557. [CrossRef]
23. Tobler, I.; Franken, P. Sleep homeostasis in the guinea-pig—Similar response to sleep-deprivation in the light and dark period. *Neurosci. Lett.* **1993**, *164*, 105–108. [CrossRef]
24. Tobler, I.; Franken, P.; Jaggi, K. Vigilance states, EEG spectra, and cortical temperature in the guinea pig. *Am. J. Physiol.* **1993**, *264*, R1125–R1132. [CrossRef]
25. Dijk, D.J.; Czeisler, C.A. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J. Neurosci.* **1995**, *15*, 3526–3538. [CrossRef]

26. Daan, S.; Beersma, D.G.M.; Borbely, A.A. Timing of human sleep—Recovery process gated by a circadian pacemaker. *Am. J. Physiol.* **1984**, *246*, R161–R178. [CrossRef]
27. Achermann, P. Technical note: A problem with identifying nonlinear interactions of circadian and homeostatic processes. *J. Biol. Rhythm.* **1999**, *14*, 602–603. [CrossRef]
28. Achermann, P.; Borbely, A.A. Simulation of human sleep—Ultradian dynamics of electroencephalographic slow-wave activity. *J. Biol. Rhythm.* **1990**, *5*, 141–157. [CrossRef]
29. Achermann, P.; Beersma, D.G.M.; Borbély, A.A. The two-process model: Ultradian dynamics of sleep. In *Sleep '90*; Horne, J.A., Ed.; Pontenagel Press: Bochum, Germany, 1990; pp. 296–300.
30. Achermann, P.; Dijk, D.J.; Brunner, D.P.; Borbely, A.A. A model of human sleep homeostasis based on EEG slow-wave activity—Quantitative comparison of data and simulations. *Brain Res. Bull.* **1993**, *31*, 97–113. [CrossRef]
31. Tobler, I. Effect of forced locomotion on the rest activity cycle of the cockroach. *Behav. Brain Res.* **1983**, *8*, 351–360. [CrossRef]
32. Tobler, I.; Neunerjehle, M. 24-h variation of vigilance in the cockroach Blaberus-giganteus. *J. Sleep Res.* **1992**, *1*, 231–239. [CrossRef]
33. Tobler, I.; Stalder, J. Rest in the scorpion—A sleep-like state. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* **1988**, *163*, 227–235. [CrossRef]
34. Franken, P.; Dijk, D.J.; Tobler, I.; Borbely, A.A. Sleep-deprivation in rats—Effects on EEG power spectra, vigilance states, and cortical temperature. *Am. J. Physiol.* **1991**, *261*, R198–R208. [CrossRef]
35. Hendricks, J.C.; Finn, S.M.; Panckeri, K.A.; Chavkin, J.; Williams, J.A.; Sehgal, A.; Pack, A.I. Rest in Drosophila is a sleep-like state. *Neuron* **2000**, *25*, 129–138. [CrossRef]
36. Shaw, P.J.; Cirelli, C.; Greenspan, R.J.; Tononi, G. Correlates of sleep and waking in Drosophila melanogaster. *Science* **2000**, *287*, 1834–1837. [CrossRef]
37. Nath, R.D.; Bedbrook, C.N.; Abrams, M.J.; Basinger, T.; Bois, J.S.; Prober, D.A.; Sternberg, P.W.; Gradinaru, V.; Goentoro, L. The jellyfish Cassiopeia exhibits a sleep-like state. *Curr. Biol.* **2017**, *27*, 2984–2990.e3. [CrossRef]
38. Kanaya, H.J.; Park, S.; Kim, J.; Kusumi, J.; Krenenou, S.; Sawatari, E.; Sato, A.; Lee, J.; Bang, H.; Kobayakawa, Y.; et al. A sleep-like state in the Hydra unravels conserved sleep mechanisms during the evolutionary development of the central nervous system. *Sci. Adv.* **2020**, *6*, eabb9415. [CrossRef]
39. Moruzzi, G. Sleep-waking cycle. *Ergeb. Physiol. Biol. Chem. Exp. Pharmakol.* **1972**, *64*, 1–165.
40. Krueger, J.M.; Obal, F. A neuronal group-theory of sleep function. *J. Sleep Res.* **1993**, *2*, 63–69. [CrossRef]
41. Kattler, H.; Dijk, D.J.; Borbely, A.A. Effect of unilateral somatosensory stimulation prior to sleep on the sleep EEG in humans. *J. Sleep Res.* **1994**, *3*, 159–164. [CrossRef]
42. Huber, R.; Ghilardi, M.F.; Massimini, M.; Tononi, G. Local sleep and learning. *Nature* **2004**, *430*, 78–81. [CrossRef]
43. Vyazovskiy, V.; Borbely, A.A.; Tobler, I. Unilateral vibrissae stimulation during waking induces interhemispheric EEG asymmetry during subsequent sleep in the rat. *J. Sleep Res.* **2000**, *9*, 367–371. [CrossRef] [PubMed]
44. Vyazovskiy, V.V.; Welker, E.; Fritschy, J.M.; Tobler, I. Regional pattern of metabolic activation is reflected in the sleep EEG after sleep deprivation combined with unilateral whisker stimulation in mice. *Eur. J. Neurosci.* **2004**, *20*, 1363–1370. [CrossRef] [PubMed]
45. Vyazovskiy, V.V.; Tobler, I. Handedness leads to interhemispheric EEG asymmetry during sleep in the rat. *J. Neurophysiol.* **2008**, *99*, 969–975. [CrossRef] [PubMed]
46. Tobler, I.; Jaggi, K. Sleep and EEG spectra in the Syrian-hamster (*Mesocricetus-auratus*) under baseline conditions and following sleep deprivation. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* **1987**, *161*, 449–459. [CrossRef] [PubMed]
47. Deboer, T.; Franken, P.; Tobler, I. Sleep and cortical temperature in the Djungarian hamster under baseline conditions and after sleep deprivation. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* **1994**, *174*, 145–155. [CrossRef] [PubMed]
48. Huber, R.; Deboer, T.; Tobler, I. Effects of sleep deprivation on sleep and sleep EEG in three mouse strains: Empirical data and simulations. *Brain Res.* **2000**, *857*, 8–19. [CrossRef] [PubMed]
49. Tobler, I.; Gaus, S.E.; Deboer, T.; Achermann, P.; Fischer, M.; Rulicke, T.; Moser, M.; Oesch, B.; McBride, P.A.; Manson, J.C. Altered circadian activity rhythms and sleep in mice devoid of prion protein. *Nature* **1996**, *380*, 639–642. [CrossRef] [PubMed]
50. Tobler, I.; Deboer, T.; Fischer, M. Sleep and sleep regulation in normal and prion protein-deficient mice. *J. Neurosci.* **1997**, *17*, 1869–1879. [CrossRef]
51. Tobler, I.; Deboer, T. Sleep in the blind mole rat Spalax Ehrenbergi. *Sleep* **2001**, *24*, 147–154. [CrossRef]
52. Tobler, I.; Herrmann, M.; Cooper, H.M.; Negroni, J.; Nevo, E.; Achermann, P. Rest-activity rhythm of the blind mole rat Spalax ehrenbergi under different lighting conditions. *Behav. Brain Res.* **1998**, *96*, 173–183. [CrossRef]
53. Tobler, I.; Scherschlicht, R. Sleep and EEG slow-wave activity in the domestic cat—Effect of sleep deprivation. *Behav. Brain Res.* **1990**, *37*, 109–118. [CrossRef]
54. Tobler, I.; Franken, P.; Scherschlicht, R. Sleep and EEG spectra in the rabbit under baseline conditions and following sleep deprivation. *Physiol. Behav.* **1990**, *48*, 121–129. [CrossRef] [PubMed]
55. Tobler, I.; Sigg, H. Long-term motor-activity recording of dogs and the effect of sleep deprivation. *Experientia* **1986**, *42*, 987–991. [CrossRef] [PubMed]
56. Tobler, I.; Borbely, A.A. Effect of rest deprivation on motor-activity of fish. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* **1985**, *157*, 817–822. [CrossRef] [PubMed]

57. Tobler, I.; Ruhlé, C.; Hindenlang, K. Long-term rest-activity recording in two female Ibex (Capra Ibex) in the wild. *J. Sleep Res.* **1994**, *3*, 255.
58. Tobler, I. Behavioral sleep in the asian elephant incaptivity. *Sleep* **1992**, *15*, 1–12.
59. Tobler, I.; Schwierin, B. Behavioural sleep in the giraffe (*Giraffa camelopardalis*) in a zoological garden. *J. Sleep Res.* **1996**, *5*, 21–32. [CrossRef]
60. Hess, W.R. The autonomic nervous system. *Lancet* **1932**, *2*, 1259–1261. [CrossRef]
61. Franken, P.; Tobler, I.; Borbély, A.A. Sleep and waking have a major effect on the 24-hr rhythm of cortical temperature in the rat. *J. Biol. Rhythm.* **1992**, *7*, 341–352. [CrossRef]
62. Sela, Y.; Hoekstra, M.M.B.; Franken, P. Sub-minute prediction of brain temperature based on sleep-wake state in the mouse. *Elife* **2021**, *10*, e62073. [CrossRef]
63. Adamantidis, A.R.; de Lecea, L. Sleep and the hypothalamus. *Science* **2023**, *382*, 405–412. [CrossRef]
64. Franken, P.; Dijk, D.J. Sleep and circadian rhythmicity as entangled processes serving homeostasis. *Nat. Rev. Neurosci.* **2024**, *25*, 43–59. [CrossRef] [PubMed]
65. Abhilash, L.; Shafer, O.T. A two-process model of Drosophila sleep reveals an inter-dependence between circadian clock speed and the rate of sleep pressure decay. *Sleep* **2023**. [CrossRef] [PubMed]
66. Skeldon, A.C.; Dijk, D.J. Modelling Drosophila sleep: Fly in the sky? *Sleep* **2023**. [CrossRef] [PubMed]
67. Thomas, C.W.; Guillaumin, M.C.C.; McKillop, L.E.; Achermann, P.; Vyazovskiy, V.V. Global sleep homeostasis reflects temporally and spatially integrated local cortical neuronal activity. *Elife* **2020**, *9*, e54148. [CrossRef]
68. Vyazovskiy, V.V.; Olcese, U.; Hanlon, E.C.; Nir, Y.; Cirelli, C.; Tononi, G. Local sleep in awake rats. *Nature* **2011**, *472*, 443–447. [CrossRef]
69. Guthrie, R.S.; Ciliberti, D.; Mankin, E.A.; Poe, G.R. Recurrent Hippocampo-neocortical sleep-state divergence in humans. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2123427119. [CrossRef]
70. Nobili, L.; Ferrara, M.; Moroni, F.; De Gennaro, L.; Lo Russo, G.; Campus, C.; Cardinale, F.; De Carli, F. Dissociated wake-like and sleep-like electro-cortical activity during sleep. *Neuroimage* **2011**, *58*, 612–619. [CrossRef]