Behavioral and Electrophysiological Correlates of Sleep and Sleep Homeostasis

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Abstract The definition of what sleep is depends on the method that is applied to record sleep. Behavioral and (electro)-physiological measures of sleep clearly overlap in mammals and birds, but it is often unclear how these two relate in other vertebrates and invertebrates. Homeostatic regulation of sleep, where the amount of sleep depends on the amount of previous waking, can be observed in physiology and behavior in all animals this was tested in. In mammals and birds, sleep is generally subdivided into two states, non-rapid eye movement (NREM) sleep and REM sleep. In mammals the combination of behavioral sleep and the changes in the slow-wave range of the NREM sleep electroencephalogram (EEG) can explain and predict the occurrence and depth of sleep in great detail. For REM sleep this is far less clear. Finally, the discovery that slow-waves in the NREM sleep EEG are influenced locally on the cortex depending on prior waking behavior is an interesting new development that asks for an adaptation of the concept of homeostatic regulation of sleep. Incorporating local sleep into models of sleep regulation is needed to obtain a comprehensive picture.

Keywords Sleep · Mammals · Birds · Behavior · Electroencephalography · Sleep homeostasis · Local sleep · Function of sleep

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Contents

1 What is Sleep?

1.1 Sleep is a Behavior: Rest and Activity

Before we can try to understand the basics of sleep and wakefulness, it should first be clear what is meant when the words 'wakefulness' and 'sleep' are used. In the most general description, wakefulness is a (daily recurring) state of the brain in which an individual organism engages in coherent cognitive and behavioral responses to the external world. These responses consist of (among others), locomotor activity, the ingestion of nutrients, reproduction, and communication. In most of these, sleep is the opposite of wakefulness. All we can see from the outside, when an animal is asleep, is that it is inactive. However, there are certain features of this inactive state that distinguish it from other inactive conditions. These include behavioral features proposed by Pieron (1913) with later additions made by Flanigan (1972) and Tobler (1984). During sleep, animals show a reduced reaction to stimuli, which distinguishes sleep from quiet wakefulness. However, this situation is easily reversed, which distinguishes sleep from other inactive states like hibernation, coma, or death. In addition, sleep as a behavior typically occurs at a species specific time of day, at a specific site and in a specific posture.

Based on these features, sleep-like behavior can be identified and investigated in many different species in the animal kingdom. Sleep as a resting state in invertebrates is investigated in great detail in bees and fruit flies, but also other insects and animals from other invertebrate phyla have been investigated (in the past reviewed by Campbell and Tobler 1984). Specific sleep postures and sleep sites have been described in the marine mollusk *Aplysia* (Strumwasser 1971), and in many insect species (Fiebrig 1912; Pittioni 1933; Rau 1938; Rau and Rau 1916; Sharplin 1963; Young 1935). The specific sleep postures were associated with an elevated arousal threshold in *Octopus vulgaris* (Lafont 1870), scorpions (Tobler and Stalder 1988), moths (Andersen 1968), and other insects (Blest 1958, 1960a, b).

Detailed research in bees showed that these animals show the complete spectrum of behavioral changes encompassing sleep, similar as in birds and mammals (Kaiser 1988; Sauer et al. 2004), but that they also show similar changes in physiology. These latter changes include a decrease in body temperature and muscle tone (Kaiser 1988) and changes in neuronal activity (Kaiser and Steinerkaiser 1983), showing that all these changes may be universal for sleep.

The last decades, the fruit fly (*Drosophila)* is by far the most intensely investigated invertebrate species in sleep research. Particularly, since the start of this century, the genetics of sleep has driven the development of different automated rest-activity recording methods for drosophila (ultrasound, camera tracking, or movement detection) to such heights that these variables in this species can now be monitored in great detail. It was shown, that drosophila not only shows a typical site and posture with increased arousal threshold during sleep-like behavior, but that it is modulated by stimulants and hypnotics, in a similar way as in mammals (Hendricks et al. 2000; Shaw et al. 2000).

Also in vertebrate species, automated rest-activity recordings are applied to determine sleep-like behavior. They are an important supporting tool in sleep research as they are non-invasive and relatively easy to use for a longer period of time with many subjects participating simultaneously. Actigraphy, with a wrist-worn monitor, is the standard procedure to observe rhythms in human subjects when entering a sleep experiment, or to perform a preliminary screen for sleep or circadian rhythm pathology in patients with sleep disorders (Ancoli-Israel et al. 2003). Actigraphy can also be used on children and infants, for instance to monitor the development of day–night rhythms (Jenni et al. 2006). Another application of actigraphy is the recording of long-term rest-activity rhythms in larger animals under natural conditions, for instance reindeer under polar light conditions (van Oort et al. 2005).

In genetically manipulated mice, rest-activity recordings have also become an important tool as a preliminary screen for changes in sleep and circadian rhythms. Rodents cannot carry an actigraph, and therefore, their rest-activity behavior is usually monitored by automated recording of running wheel activity rotations. As these recordings are influenced by several environmental cues [i.e., availability and size of the wheel, availability and quality of light (Banjanin and Mrosovsky 2000; Deboer and Tobler 2000a; Kas and Edgar 1999; Mrosovsky et al. 1998)], it is important to perform wheel-running experiments under well-defined environmental conditions. For instance, it has been shown that the availability of a running wheel influences the occurrence and distribution of sleep (Vyazovskiy et al. 2006). Another method to record activity patterns is by using passive infrared (PIR) detectors. The PIR detector is adapted from the infrared sensors normally placed above automatic sliding doors. It is placed above the cage and detects movement of the animals due to changes in the distribution of heat radiation in the cage. It can therefore only detect movement of euthermic animals. Recently video recording setups, which automatically score sleep-wake behavior, have been developed. Under well-defined circumstances, a high correlation with electroencephalogram (EEG) confirmed sleep can be achieved (Fisher et al. 2012; McShane et al. 2012).

With some additional quantification even REM sleep may be assessed (McShane et al. 2012), although the success rate of the latter is lower and needs further confirmation.

All of these methods are advantageous for high-throughput screening, but not for a detailed analysis of sleep. For vertebrates, particularly mammals and birds, there is another method to determine vigilance states, which depends on recording the electrical activity in the cortex (electroencephalography) together with other physiological variables (muscle activity, eye movements), and defines sleep states as different physiological states of the brain (see *Sleep is a brain state*). There seems to be a close correlation between the recorded rest-activity profile obtained from PIR or video, and the occurrence of electroencephalographic confirmed sleep and wakefulness (Farajnia et al. 2012; Fisher et al. 2012; McShane et al. 2012). However, there is not always a strong correlation between running wheel activity and sleep (Antle et al. 2012).

The intensity or depth of sleep can vary over time (see *Sleep is a brain state*). Until now, behavioral observations cannot provide a measure for the intensity or depth of the recorded rest or sleep [but see the cockroach for a possible exception (Tobler and Neuner-Jehle 1992)]. Only by determining the arousal threshold, and by that disturbing the animal, it is possible to get a measure for the depth of sleep. By comparing arousal thresholds with the EEG patterns, it is possible in mammals to overcome some of these limitations.

1.2 Sleep is a Brain State: The Electroencephalogram

The discovery of electrical activity of the brain in the 1870s (Caton 1875, 1877) was an important breakthrough in brain research. It laid the foundation for the development of the EEG by Hanns Berger (1929) and eventually modern polysomnography (PSG).

The EEG is a record of the fluctuations of electrical activity of the brain, which is recorded from the surface of the scalp. It is used to distinguish sleep states but also for diagnostics of cerebral dysfunctions. To record the EEG, a minimum of two electrodes are necessary. The active electrode is placed above the area of interest and an indifferent electrode is placed at a distance. The majority of the recorded signals originate from extracellular current flow, associated with the summed post-synaptic activity in synchronously activated vertically oriented pyramidal cells. When recording human sleep, both in research and in the clinic, many electrodes are placed on well-described areas of the head according to a conventional scheme (Keenan and Hirshkowitz 2011). The major frequencies recorded from the scalp during a normal sleep recording vary between 0.1 and 50 Hz and the amplitudes typically range between 20 and 300 μV. The frequency and amplitude characteristics of the EEG are rather complex, and may vary in the course of a recording session. However, a few dominant frequencies can be observed in the human EEG (Fig. 1). They are named after letters of the Greek

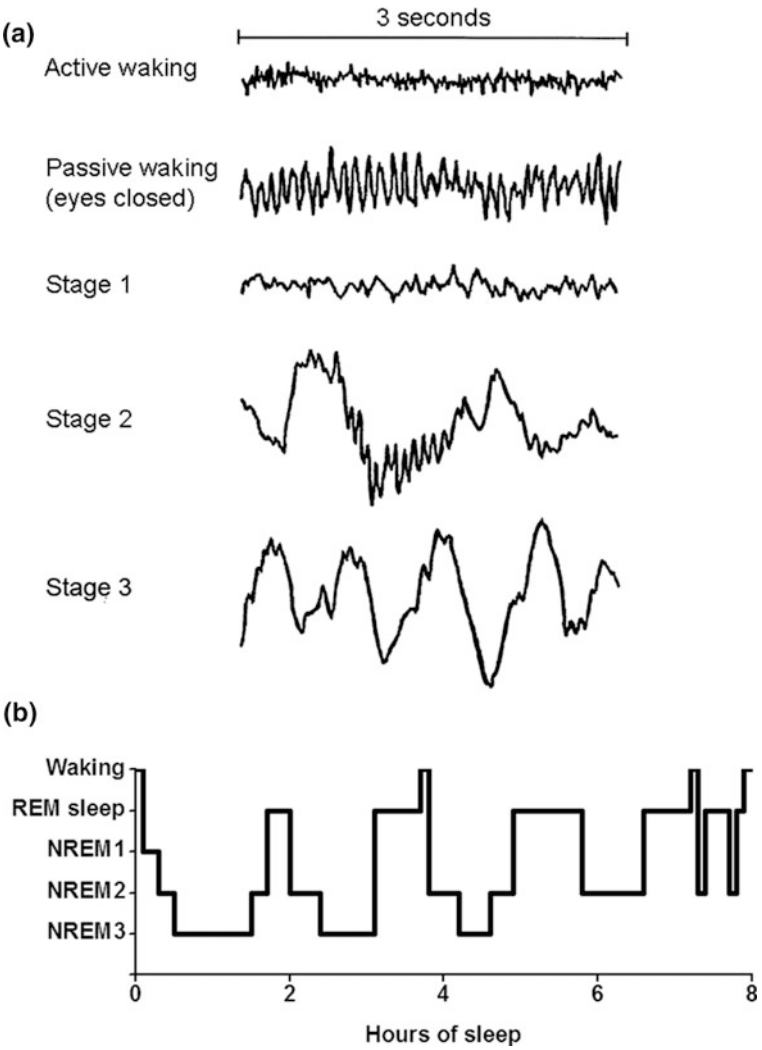

Fig. 1 **a** Detailed 3 s electroencephalographic records with specific features visible during certain sleep stages in humans with (from *top* to *bottom*), Beta-activity during active waking, alpha activity during waking with eyes closed, theta activity during NREM sleep stage 1, K-complex and spindle activity (12–15 Hz) during stage 2, and delta activity during stage 3. **b** Schematic hypnogram of a normal human night sleep, with waking, the three NREM sleep states and REM sleep. Note the predominance of deep NREM sleep (NREM3) with high amplitude slow-waves at the beginning of the night and the long REM sleep episodes at the end of the night

alphabet. Alpha waves (8–13 Hz) are mainly visible during relaxed waking with eyes closed. These are the first EEG waves distinguished by Hanns Berger (1929). Beta waves (13–30 Hz) are mainly visible during normal waking. Delta waves

(0.5–4.0 Hz) are visible during deep non-rapid eye movement (NREM) sleep, whereas theta waves (4–7 Hz) are visible during the first stage of NREM sleep. During the initial stages of sleep, at the transition to deep NREM sleep in humans, also K-complexes (a sharp single slow-wave) and spindles (a short burst of 12–15 Hz) can be observed.

Modern day PSG in humans combines the recording of the EEG with recording of muscle activity (electromyography, EMG), eye movements (electrooculography, EOG), heart rate (electrocardiogram, ECG), and respiration, but the EEG remains the backbone of sleep research in humans. Since the end of the 1960s, sleep staging in humans was mainly done according to the definitions of Rechtschaffen and Kales (1968) with one waking state, four NREM sleep states, and REM sleep. In 2007, the American Academy of Sleep Medicine (AASM) published a manual with new recommendations for recording methods and terminology (Iber et al. 2007). In this manual, the deep states of NREM sleep (states 3 and 4) are lumped together in one NREM sleep state (state 3 or slow-wave sleep; SWS). In addition, the manual contains rules for arousal, cardiac, movement, and respiratory events which add value to the clinical assessment of sleep disturbances and sleep-related illnesses. However, the specifications given by the AASM for recording and scoring of normal healthy sleep are not without controversy (Danker-Hopfe et al. 2009; Miano et al. 2010; Moser et al. 2009; Novelli et al. 2010). With these specifications for sleep state scoring it is possible to provide a record of the sleep-wake architecture over an entire night (Fig. 1b).

In other mammals and birds, in general, three states (waking, NREM sleep, and REM sleep) are distinguished. In Fig. 2, examples are given for EEG and EMG recordings in a mouse for the three vigilance states. With the electrode placement in mice, as described previously (Deboer et al. 2007b, 2013; Huber et al. 2000a), the EEG predominantly shows theta activity ($\sim$ 7 Hz) during waking and REM sleep, whereas in NREM sleep, high amplitude slow-waves ($<$ 5 Hz) predominate. During sleep EMG levels are low, whereas during waking EMG activity is higher. In some animal studies, NREM sleep is divided into deep NREM sleep, with high amplitude slow-waves and light NREM sleep with a lower EEG amplitude. In studies interested in REM sleep regulation or REM sleep-related phenomena, an intermediate or transitional state between NREM and REM sleep may be identified (Deboer et al. 1998; Gottesmann 1996). Although the vigilance states waking, NREM sleep, and REM sleep show large similarities in their behavior between mammalian species, the EEG and its spectral composition (Fig. 2, right panels) may differ (compare for instance human EEG (Borbely et al. 1981) with rat EEG (Borbely et al. 1984)). The latter may be due to differences between species in brain anatomy, but also because electrodes may not always be positioned at similar anatomical sites of the different species.

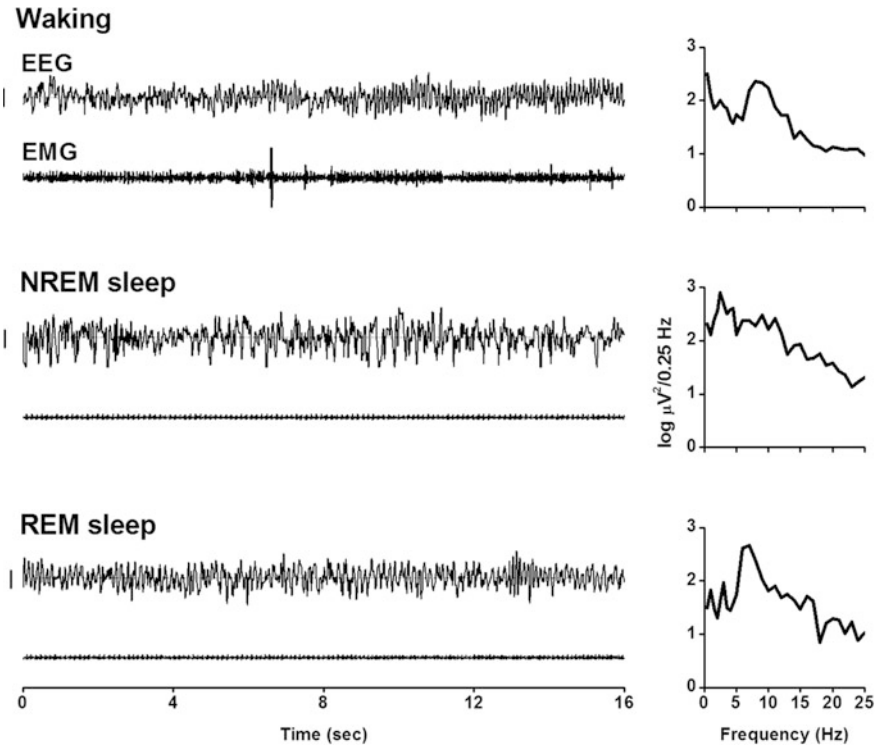

Fig. 2 *Left panels*Detailed electroencephalogram (EEG) and electromyogram (EMG) traces of 16 s of a mouse. Classification of the vigilance states is based on the visual inspection of both signals. Note the low activity, with heart rate, in the EMG in both sleep states. During waking, EMG activity is high and the EEG shows high theta (∼7 Hz) activity. *Right panels* Spectral analysis of the corresponding EEG traces in the *left panel* by a fast Fourier Transform routine. Spectral analysis is a mathematical approach to quantify the composition of complex waveforms with the purpose to decompose the complex signal into its single frequency components. Applied to the EEG it provides the opportunity to not just recognize the different vigilance states and the corresponding dominant frequencies in the EEG (*left panels*, and Fig. 1) but the whole spectral composition of the EEG (*right panels*). Indicated is the average power density spectrum of the four 4-s epochs in the *left panel* in 30 frequency bins between 0.25 and 25 Hz plotted on a logarithmic scale. The slow-waves during NREM sleep are reflected by high activity in the delta band (below 4 Hz). REM sleep and waking are characterized by dominant activity in the theta band (5.25–7.0 Hz)

2 Sleep Homeostasis

2.1 Homeostasis of Sleep Behavior

As mentioned previously, sleep as a behavior can be distinguished from other similar states like coma, hibernation, and death through different sleep specific features. In addition, some kind of regulatory capacity to sleep can be observed.

When sleep is lost, this loss is, at least partly, compensated by extending and/or deepening subsequent sleep. This homeostatic aspect is thought to be one of the main regulatory processes in sleep and seems to be universal, as it is found in many different phyla of the animal kingdom. For instance, in many invertebrate species, like cockroaches, drosophila, bees, and scorpions an increase in rest was observed after rest deprivation, suggesting compensation after sleep loss (Hendricks et al. 2000; Sauer et al. 2004; Shaw et al. 2000; Tobler and Neuner-Jehle 1992; Tobler and Stalder 1988). In birds similar observation of increased sleep after sleep loss was done (Bobbo et al. 2008; Boerema et al. 2003; Tobler and Borbely 1988). Figure 3 illustrates this homeostatic response in a mammal. It shows the average hourly values of NREM sleep and REM sleep in a group of rats during a baseline day, and during and after they are subjected to a 6 h sleep deprivation. In the hours following the sleep deprivation, both NREM sleep and REM sleep values are enhanced above corresponding baseline levels. Similar data are obtained in different sleep laboratories with several different sleep deprivation and recording methods in different species, vertebrate, and invertebrate [for some other examples see (Deboer et al. 1994; Franken et al. 1991a; Hasan et al. 2012; Huber et al. 2000a, b; Shaw 2003)]. In monophasic sleeping species, like humans, the amount of sleep per hour is usually not much increased after sleep deprivation, but sleep is significantly extended. Despite this difference, all species show the same phenomenon of increased sleep. Another similarity between species is that the recovery of the amount of sleep is not complete. In the example in Fig. 3, the panels on the right show the amount of NREM sleep and REM sleep lost and regained during the 6-h sleep deprivation and subsequent 18-h recovery. Due to the sleep deprivation, the animals lose, on average, almost 200 min of NREM sleep and 50 min of REM sleep, but they do not regain this loss in the subsequent recovery. In the course of the dark period, the animals still lack 100 min of NREM sleep and 10–15 min of REM sleep, which is not recovered. If there is a sleep homeostatic response it does not involve complete homeostasis of the amount of sleep. Either it is incomplete homeostasis or there must be other ways of recovery instead.

2.2 Homeostasis in the NREM Sleep EEG

From almost the earliest days of EEG sleep research it was clear that a positive correlation exists between depth of sleep, measured by the duration and intensity needed for a sound to wake the subject or animal, and the prominence of slow-waves (< 5 Hz) in the NREM sleep EEG (Blake and Gerard 1937; Ferrara et al. 1999; Neckelmann and Ursin 1993; Rosa and Bonnet 1985; Williams et al. 1964). By applying a fast Fourier transform (see Fig. 2) to the EEG, delta activity or slow-wave activity (SWA, EEG power density between ~ 1 and 4 Hz) can be calculated and quantified. In all mammals with a clear main sleep and wake period (either diurnal or nocturnal), slow-waves in the NREM sleep EEG are prominent at the beginning of the main sleep period and SWA gradually decreases as sleep progresses. Moreover,

despite a few exceptions where the sleep deprivation may have been too stressful (Tobler and Jaggi 1987), in most mammalian and some bird species investigated, SWA in NREM sleep increases after sleep deprivation (reviewed in Deboer 2007; Rattenborg et al. 2009). Both are illustrated in Fig. 3 in the left bottom panel. Mammals seem to compensate for sleep loss by two different strategies. The amount of NREM sleep is increased, but also SWA in NREM sleep is increased. It proofed to be worthwhile to calculate a combined measure of cumulated SWA over time by multiplying NREM sleep SWA with NREM sleep time. The result is cumulative slow-wave energy (SWE, Fig. 3 right bottom panel). Although debated over with long or complex sleep deprivation protocols (Kim et al. 2007; Leemburg et al. 2010), the data after short sleep deprivations show that SWE lost during sleep deprivation can be totally recovered within a couple of hours. Finally, in humans it was shown that a nap of sufficient duration during the day decreases subsequent SWA in NREM sleep during the following night (Werth et al. 1996b).

In some mammalian species, a dose response relationship between waking duration and subsequent SWA in NREM sleep was established. An overview of these studies is shown in Fig. 4. Most species show an increase in SWA which depends on the prior sleep deprivation duration. However, there is a species specific difference in the speed of increase. Of the seven documented species, the Djungarian hamster is the animal with the fastest increase, whereas the tree shrew is the slowest and does not seem to show an increase with increasing time awake. The increase rates of the Wistar rat and European ground squirrel are similar to each other and also the increase rate of the cat and mouse are similar. Although not all data and species seem to be in a line with this idea, it has been suggested that there is a relation between the waking induced increase rate of SWA in NREM sleep and body or brain size of these species (Deboer et al. 1994). The odd ones out are the C57BL/6 mouse and the tree shrew. The latter indicates that other factors also play a role, but attempts to correlate sleep time over different species with various other parameters did not support any sleep physiological theory (Siegel 2005, 2009). Comparison between mouse strains suggests a genetic component for the build-up rate of sleep pressure (Franken et al. 2001; Huber et al. 2000a). More data, including more species, are needed to obtain a clearer picture.

Most of these results indicate that there is some kind of process which keeps track of the prior duration of sleep and waking. The level of this process is reflected in SWA of the NREM sleep EEG, and the changes in SWA are predictable. This invites the application of mathematical modeling and simulations of the homeostatic sleep response. Until now, they have been applied successfully in human (Achermann et al. 1993), rat (Franken et al. 1991b) and mouse (Franken et al. 2001; Huber et al. 2000a). Yet, although major progress has been made in our knowledge of how the slow-waves in the NREM sleep EEG are produced by the brain (Amzica and Steriade 1998; Timofeev et al. 2012), still little is known about how and why they are homeostatically regulated. It is generally accepted that the slow-waves somehow reflect sleep need and therefore provide a window on the function of sleep. However, what this function is, and whether there is a central sleep homeostat in the brain, remains a topic of research and debate.

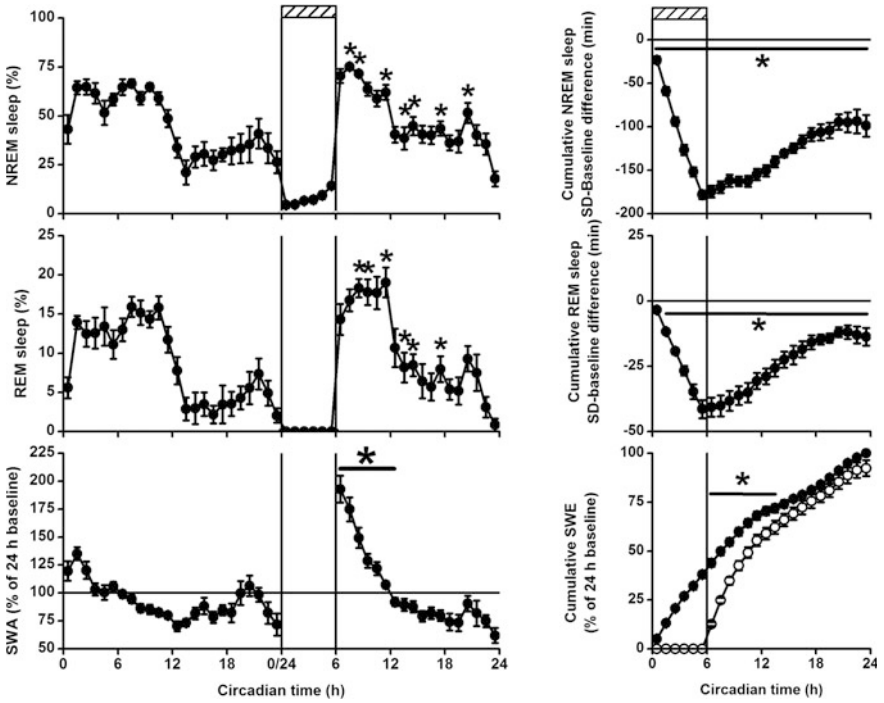

Fig. 3 *Left panels* Time course of 48 h of non-rapid eye movement (NREM) sleep, REM sleep, and slow-wave activity (SWA; EEG power density between 1 and 4 Hz) in NREM sleep across a baseline day, during a sleep deprivation performed during the first 6 h of the rest period (hatched bar at the *top*), and 18-h recovery in 1-h mean values (± SEM, $n = 11$). The recordings were obtained after 7 days adaptation to constant darkness. The vigilance states are expressed as a percentage of total recording time (= 100 %). SWA is expressed as the average over 24-h baseline (= 100 %). *Asterisks* and *solid lines* indicate where recovery significantly differed from baseline ($p < 0.05$, two-tailed paired *t*-test after significant ANOVA factor *day*). *Right top and middle panel* Cumulative NREM and REM sleep lost or gained. Plots are calculated by subtracting the minutes of sleep during deprivation (hatched bar at the *top*) and recovery from the corresponding baseline value and summing the difference with the preceding hour. Note that a significant part of the NREM sleep and REM sleep lost is not recovered. *Asterisks* and *solid lines* indicate where the sleep deprivation and recovery significantly differ from baseline ($p < 0.05$, two-tailed paired *t*-test after significant ANOVA). *Right bottom panel* Cumulative slow-wave energy (SWA*NREM sleep) for baseline (*dots*) and sleep deprivation/recovery (*circles*). Plots are calculated by summing the SWE with the previous hour. SWE is expressed as the total SWE over the 24-h baseline day (= 100 %). Note that SWE lost during the sleep deprivation is virtually totally recovered in the course of the recovery period. *Asterisks* and *solid lines* indicate where the recovery significantly differs from baseline ($p < 0.05$, two-tailed paired t-test after significant ANOVA factor *day*)

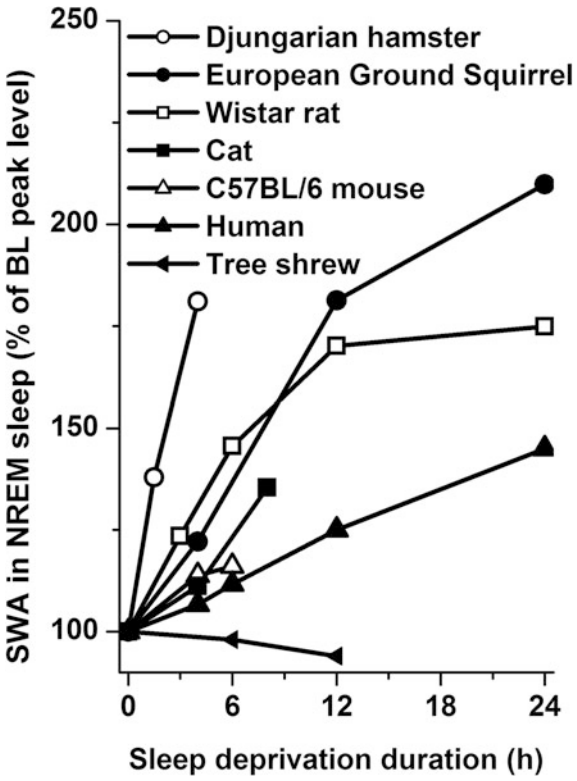

Fig. 4 Slow-wave activity (SWA; EEG power density between 1 and 4 Hz) in NREM sleep as a function of prior sleep deprivation duration in seven mammalian species. Animals were sleep deprived from the start of their main rest period when baseline SWA reaches its highest point. Data are plotted relative to this maximum baseline value. Note the difference in increase rate between the different species. Data of Djungarian hamster adapted from Deboer and Tobler (2003), C57BL/6 mouse from Huber et al. (2000a), Wistar rat from Tobler and Borbely (1986), European Ground Squirrel from Strijkstra and Daan (1998), Human from Akerstedt and Gillberg (1986), Cat from Lancel et al. (1991), and tree shrew from Coolen et al. (2012). Note the slower increase in SWA as brain and/or body size increases with the exception of the C57BL/6 mouse and the tree shrew

2.3 Changes in NREM Sleep Slow-Waves Independent of Waking Duration

Although, there is a clear relationship between waking duration and SWA in subsequent NREM sleep, several observations indicate that the occurrence of slow-waves in the NREM sleep EEG can change independent of waking duration. For instance, in infants, SWA in NREM sleep follows an alternating pattern, with high SWA in every second NREM sleep episode, independent of prior waking (Jenni et al. 2004). Also well documented is that the amplitude of slow-waves, and

therefore SWA decreases in the course of puberty (Campbell et al. 2012; Kurth et al. 2010). In the elderly, the amplitude of slow-waves further decreases (Dijk et al. 1989, 1999; Landolt et al. 1996). These changes in the expression of slow-waves in the course of puberty and adult aging all occur without affecting sleep homeostatic responsiveness.

Also the quality of sleep and waking may be influencing SWA. Disturbed sleep reduces the ability to produce high amplitude slow-waves in the NREM sleep EEG (Deboer et al. 2003; Dijk and Beersma 1989; Endo et al. 1997, 1998). In albino rats, light during the main sleep/rest period suppresses SWA in NREM sleep (Tobler et al. 1994). However, in pigmented mice such an influence was not observed (Deboer et al. 2007b), suggesting that pigmentation or light sensitivity may be the determining factor in this influence of light on slow-waves. That the quality of waking may influence subsequent slow-waves was shown by, for example, Meerlo et al. (1997). Rats that were exposed to a brief period of intense social stress, i.e., had an encounter with an aggressive dominant conspecific, showed an increase in SWA during subsequent NREM sleep. This increase was larger than the level normally obtained after non-stressful sleep deprivation of similar duration. The authors speculated that the stressful social encounter may have represented a period of intense wakefulness causing a more rapid build-up of sleep debt.

Even the time of day where the spontaneous or induced waking occurs, seems to influence the subsequent SWA response in the NREM sleep EEG (Deboer 2009; Vyazovskiy et al. 2007; Werth et al. 1996b). This suggests an influence of the endogenous circadian clock on the expression of slow-waves, either indirectly by modulating the quality of waking in a circadian pattern, or directly by influencing the expression of slow-waves in the EEG.

Pharmacological manipulations can also influence the expression of slow-waves. Caffeine is well known to increase alertness during the day. In addition, it was shown in humans and animals that it also delays sleep onset and reduces SWA during subsequent NREM sleep (Deboer et al. 2013; Landolt et al. 1995a, b; Schwierin et al. 1996). Caffeine is thought to influence sleep propensity by blocking the adenosine receptors. In accordance with that, stimulating the adenosine A1 receptor increases sleep and SWA in NREM sleep (Benington et al. 1995; Deboer et al. 2013; Schwierin et al. 1996).

There are several other pharmacological manipulations that also influence sleep and SWA. Atropine induces high amplitude slow-waves without affecting sleep (Bringmann 1995; Schaul et al. 1978). Benzodiazepines increase NREM sleep, but reduce slow-waves (Bastien et al. 2003). Other substances enhance NREM sleep duration and SWA simultaneously, like tumor necrosis factor, growth hormone releasing hormone, and interleukin-1 (Obal and Krueger 2003). Others decrease SWA, but still increase the amount of NREM sleep, like nerve growth factor, neurotropin-4, and obestatin (Szentirmai and Krueger 2006). Not all pharmacological agents which influence the occurrence of sleep or SWA in the NREM sleep EEG are related to normal physiological changes in sleep or sleep pressure. For instance, gamma-hydroxybutyrate does not show a sleep promoting effect but at

higher doses of GHB, EEG hyper synchronization with increased SWA together with a coma-like state is observed (Meerlo et al. 2004). Therefore, always the question should be asked whether the sleep-like state seen is true physiological sleep.

The genetic makeup can also influence the occurrence and strength of SWA in NREM sleep. In humans, an influence on SWA in NREM sleep was found in polymorphisms of genes influencing the level of adenosine in intracellular space (Bachmann et al. 2012; Retey et al. 2005), and polymorphisms in the per3 gene (Viola et al. 2007). In rodents, it was already shown in the 1970s that inbred mouse strains show differences in the occurrence and amplitude of slow-waves in the NREM sleep EEG (Valatx et al. 1972). Later it was shown that mouse strains show distinct differences in their EEG power density spectra (Franken et al. 1999; Huber et al. 2000a), and some of these differences were linked to differences in the genetics between the strains (Tafti and Franken 2002).

Finally, natural hypothermic states, like daily torpor and hibernation, can also change the occurrence of slow-waves during subsequent NREM sleep. Both after daily torpor and hibernation, animals show an increase in NREM sleep and SWA (Daan et al. 1991; Deboer and Tobler 1994; Trachsel et al. 1991). Combining daily torpor with sleep deprivations, it was shown in Djungarian hamsters that the increase in SWA after torpor was genuinely sleep-wake dependent. The animals postponed their deep NREM sleep with high SWA to a later time, when a sleep deprivation was applied (Deboer and Tobler 2000b). However, in ground squirrels, a sleep deprivation after hibernation made the subsequent increase in SWA disappear, indicating that it did not reflect the usual sleep-wake dependency (Larkin and Heller 1998; Strijkstra and Daan 1998). Research into this area has come more or less to a standstill and the discrepancy between hibernation and daily torpor has not been resolved until now (reviewed in Deboer 2005). Recently, it was shown that inducing a torpid like state in rats results in increased NREM sleep and SWA after rewarming (Cerri et al. 2013), similar to the findings obtained after daily torpor or in the course of hibernation.

The list of possible influences on SWA in NREM sleep, other than the duration of prior sleep and waking duration, shows that slow-waves may not only be an expression of a sleep homeostatic process, but may depend on global or local brain circuitry which can be manipulated by pharmacological agents and behavioral changes.

2.4 Local NREM Sleep Homeostasis

The observation that the dolphin exhibits deep slow-wave sleep only in on hemisphere simultaneously (Mukhametov et al. 1977), triggered the idea that sleep homeostasis may also have a local cortical component. Interestingly, experiments with selective deprivation of unihemispheric sleep in dolphins resulted in a unihemispheric slow-wave sleep rebound (Oleksenko et al. 1992). The data showed

that sleep, and therefore the sleep homeostatic process, is not necessarily a global process, running in parallel in the entire brain. More recently, in land living mammals, it was shown that the time constants of the decrease rate of SWA and therefore the hypothetical homeostatic recovery process differs between cortical areas of the brain (Huber et al. 2000b; Palchykova et al. 2002; Rusterholz and Achermann 2011; Werth et al. 1996a, 1997). These findings supported the notion that a use-dependent local cortical mechanism may underlie the sleep deprivation induced changes in the slow-waves of the NREM sleep EEG (Benington and Heller 1995; Krueger et al. 1999).

This idea was tested in many different ways in many different mammalian species. Pioneering work by the group of Alex Borbely showed that local activation of a particular cortical area during waking results in EEG changes recorded from the same cortical area during subsequent sleep (Kattler et al. 1994). A vibratory stimulus was applied to the hand to activate the contralateral somatosensory cortex. The effect on the subsequent sleep EEG was most prominent in the slow-wave range of the EEG, and was restricted to the derivation, corresponding with the same cortical area. Subsequent research stimulating the barrel cortex via the vibrissae in mice (Vyazovskiy et al. 2004), the motor cortex with running wheel activity in mice (Vyazovskiy et al. 2006), or the use of paw preference in rats (Vyazovskiy and Tobler 2008), showed that this is probably a universal property in mammals. An elegant experiment in humans applying a motor learning task (Huber et al. 2004a), which involves a restricted part of the cortex, confirmed the notion that local cortical SWA during NREM sleep can be changed under influence of the workload during previous waking in that particular part of the cortex. Recent data in the rat show that animals that are awake, which is confirmed by the global EEG, on a local cortical level can express slow-waves of which the timing correlates with hits and misses on a reaching task (Vyazovskiy et al. 2011). Together the data indicate that the occurrence of slow-waves and their homeostatic changes can be a local cortical phenomenon.

The discovery of this local cortical homeostasis in slow-waves may have consequences for our thinking about sleep homeostasis and its relation with sleep regulatory mechanisms. Local sleep homeostasis shows that the occurrence of slow-waves, which was previously thought to be a marker for a global sleep homeostat, is influenced by use-dependent local processes. The fact that sleep regulatory models, based on SWA, have some predictive value, concerning the timing of sleep, suggests that these local changes in sleep homeostasis may be translated into a general signal influencing the switch between sleep and wakefulness. This may require that one or more brain regions involved in sleep regulation monitors local sleep homeostasis over the entire cortex. Candidate areas are those involved in sleep regulation on the neuronal level. These include histaminergic tuberomammilary nucleus (TMN) of the hypothalamus, noradrenergic cells in the locus coeruleus (LC), serotonergic cells from the dorsal raphe (DR) nucleus, and cholinergic cells in the pons (Saper et al. 2001). Next to inhibiting sleep promoting neurons in the ventrolateral preoptic area, the aminergic neurons from TMN, LC, and DR are thought to promote waking via excitation of arousal

systems in the hypothalamus, thalamus, basal forebrain (BF), and cortex. Inhibition of cholinergic neurons in the BF by release of adenosine promotes NREM sleep (Jones 2004). Alternation between NREM and REM sleep is thought to be caused by cholinergic, serotonergic, and norepinephrinergic systems in the pons, LC and DR (McCarley and Massaquoi 1992). In addition, the endogenous clock, residing in the suprachiasmatic nucleus of the hypothalamus (Meijer and Rietveld 1989) is thought to provide the sleep–wake neuronal mechanisms with a circadian framework, promoting sleep and waking at the proper time of the day.

That changes in cortical activity may influence these deeper brain areas are not as unlikely as it may seem. In the past, we have observed a correlation between the activity of neurons in the suprachiasmatic nucleus and SWA in NREM sleep (Deboer et al. 2003, 2007a). This finding shows that changes related to sleep homeostasis can also be found in the activity of neurons in deeper brain areas. For the sleep homeostatic model to work, it may require a general field detector of local cortical sleep homeostasis to be located in a brain area involved in sleep initiation and maintenance.

Whether we look at sleep as a behavior or as a physiological brain state, the homeostatic component is visible in both behavior and physiology and can be seen as a general and defining property of sleep in all animals. In mammalian and bird sleep, the analysis of changes in the sleep, EEG in relation to sleep–wake duration has become very important. The discovery of local cortical sleep-like phenomena sheds new light on sleep physiology and implementing these into models of sleep regulation is needed for a comprehensive picture of the mechanisms of sleep regulation.

2.5 REM Sleep Homeostasis, or Not?

NREM and REM sleep alternate in a cyclic pattern and the occurrence of REM sleep can be described in cyclic interaction models (McCarley and Massaquoi 1992), which results in a fairly constant ratio between NREM and REM sleep under undisturbed baseline conditions. Next to that, in humans, REM sleep is strongly influenced by the circadian clock (Carskadon and Dement 1975; Dijk and Czeisler 1995; Lavie and Scherson 1981), but in rodents this may be less the case (Yasenkov and Deboer 2010, 2012).

REM sleep often displays a rebound increase after sleep deprivation (Fig. 3; Borbely and Neuhaus 1979; Borbely et al. 1984; Dement 1960) and it is still generally believed that REM sleep recovery largely occurs through an increase in REM sleep time. However, similar to NREM sleep this recovery is generally not complete (Fig. 3). A number of studies have reported subtle changes in the REM sleep EEG following sleep deprivation, particularly in the theta frequency range, suggesting that REM sleep quality or intensity may change as well (Borbely et al. 1984; Endo et al. 1998; Tobler and Borbely 1986). However, in contrast to the well-established homeostatic regulation of NREM sleep in relation to prior

wakefulness, rebounds in REM sleep time are less predictable and may only occur after longer sleep deprivation duration. In addition, it is still debated whether REM sleep is homeostatically regulated in relation to prior waking or to prior NREM sleep (Benington and Heller 1994; Franken 2002b; Ocampo-Garces et al. 2000). The analysis of REM sleep regulation is complicated by the fact that the expression of REM sleep is also highly sensitive to modulation by various other factors. For example, brain temperature (Deboer and Tobler 1996; Parmeggiani et al. 1975), environmental temperature (Amici et al. 1998, 2008; Roussel et al. 1984), and stress (Meerlo et al. 2001; Rampin et al. 1991; Sanford et al. 2010) are shown to influence the occurrence of REM sleep. Moreover, the influence of stress is not unambiguous. Uncontrollable foot-shock stress significantly suppresses REM sleep, but with no subsequent rebound (Sanford et al. 2010). In contrast, exposure to immobilization stress, with only minor loss of REM sleep, increases subsequent REM sleep beyond baseline levels (Meerlo et al. 2001; Rampin et al. 1991).

There is still no consensus on how REM sleep is regulated and by what (Benington 2002; Franken 2002a), and this may not be resolved until we know more about the function of REM sleep or when we discover the physiological substrate of REM sleep pressure.

3 Functional Implications

Life as we know it evolved on a rotating planet. As a result, almost all species developed a timing system that shows persistent circadian oscillations, even under constant conditions. Organisms that are able to predict daily changes in temperature, radiation and food availability have an advantage over organisms that cannot predict these changes (Ouyang et al. 1998; Woelfle et al. 2004). Depending on the environmental time, the organism is active or resting. In addition, the clock needs to coordinate and streamline internal physiology to optimize energy expenditure and the use of internal recourses. During the active phase ingestion and reproduction are prominent, during rest maintenance and growth. As soon as animals developed a central nervous system, this also became part of the already existing rest-activity cycle. One can hypothesize that for maintenance this organ needs to go off-line like the rest of the body, and this condition is what we now call sleep.

In contrast to activities like, foraging, eating, drinking, and mating, the benefits of sleep are unclear. However, the costs of sleep seem to be substantial. Sleep leaves the animal defenseless for more or less a third of its life, and if it were not essential, natural selection would long since have eliminated sleep. But until now, no vertebrate has been found which does not spend a significant amount of its life asleep (Campbell and Tobler 1984). That alone is already a strong indication that sleep is important. Disruption of sleep can have large consequences for health and well-being (Aldabal and Bahammam 2011; Baglioni et al. 2011; Durmer and Dinges 2005; Meerlo et al. 2008; Spiegel et al. 2009) and prolonged sleep

deprivation may lead to death (Everson et al. 1989; Kleitman 1927; Manaceine 1894). Sleep therefore seems to fulfill an important function, which cannot be fulfilled during wakefulness. In the history of its extensive scientific study, numerous theories for the function of sleep have been proposed and rejected and no satisfactory explanation for the necessity of sleep has been offered. The fact that in mammals and birds two distinct sleep states are found supports the notion that sleep may have at least two functions, and from an evolutionary perspective there may even be many functions of sleep.

Different biological disciplines came up with different explanation for the occurrence of sleep. Sleep was suggested to reduce predatory risks at certain times of the day (Meddis 1975) or to reduce body and brain temperature, preventing overheating (McGinty and Szymusiak 1990). Also theories related to energy balance were proposed. Either sleep was for energy conservation of the organism (Berger and Phillips 1995), or restocking energy reserves of the brain specifically, which was depleted during waking (Benington and Heller 1995). For REM sleep genetic reprogramming, strengthening psychological individuality (Jouvet 1998), but also removing undesirable modes of interactions in networks of cells of the cerebral cortex (Crick and Mitchison 1983), a certain type of regulated memory loss, was proposed. More recent theories suggest an important role for sleep in neuronal plasticity, or more specific, a role in learning and memory consolidation. For the latter, a large amount of data has been produced, but a lot remains unclear, also because there are several types of memory and at least two types of sleep (reviewed in Stickgold 2013). When it comes to neuronal plasticity there are a few theories with subtle differences available. It has been proposed that sleep stimulates the use and maintenance of synaptic connections which are not (or too little) used during waking (Krueger and Obal 1993). The opposite, e.g., sleep increases the sensitivity of synapses intensely used during waking has also been proposed (Kavanau 1997). A popular recent hypothesis proposes synaptic homeostasis, where during waking synaptic potentiation occurs, followed by sleep where, during NREM sleep, synaptic downscaling takes place (Tononi and Cirelli 2003, 2006). The synaptic homeostasis hypothesis is in accordance with sleep homeostatic mechanisms, and also the data showing local cortical homeostasis of SWA are in accordance with the synaptic homeostasis hypothesis. In addition, the hypothesis may also be able to explain why sleep is beneficial for learning and memory. On the other hand, not all available data are in agreement with the synaptic homeostasis hypothesis and, as with all previous theories on the function of sleep, it is heavily debated (Frank 2012).

Understanding sleep regulation and sleep function is crucial for understanding brain functioning. It can be concluded that this requires data and ideas from different methods, models, and research areas. Although great progress was made in the last century, many questions remain unanswered. Building on a multidisciplinary approach is important to increase our understanding in the decades to come.

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