

Chapter 9

The Circadian Clock and the Homeostatic Hourglass: Two Timepieces Controlling Sleep and Wakefulness

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9.1 Introduction

Two facets of time play a pivotal role in the prediction of sleep propensity in humans: *internal* biological time and *external* time that is elapsed time spent awake and asleep [1, 2]. Briefly, *internal time* is determined by the endogenous circadian pacemaker, and needs to undergo a daily synchronization with the *external* time. On the other hand, “elapsed time” awake and asleep mirrors the homeostatic process and accumulates exponentially during wakefulness and is subsequently discharged during sleep in a faster exponential fashion.

Biological rhythms (*internal time*) comprise repetitive biological events with three main features: period, which corresponds to the length of a given rhythm; phase, which consists in the timing of a given rhythm with respect to a stimulus; and amplitude, which is the measure of the amount of a rhythmic event [3]. Circadian rhythms in humans have a period of approximately 24 h that is in tune with the 24-h solar light–dark cycle, the most important recurring stimulus in our environment [4]. Moreover, these rhythms have been recently shown to depend on genetically controlled rhythmic molecular events that rule several dimensions of cellular, system, and behavioral functions [5–7].

One fundamental behavioral circadian rhythm is the sleep–wake cycle. While wake during the diurnal period enables optimal use of vision to direct behavior, sleep during the night provides the best time for critical restorative behavior. Thus, the physiological rationale for the circadian regulation is to provide an optimal

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temporal organization for the sleep–wake cycle on several domains, such as the timing and architecture of sleep [8].

Besides this internal circadian control of the sleep–wake rhythm, the amount of time spent awake and asleep per 24 h is under a homeostatic control such that sleep propensity increases with elapsed time awake and dissipates with elapsed time asleep during the following sleep episode [9]. Independent of internal time (i.e., circadian phase), the maximal capacity to stay awake in an adult human is around 16 h, and the maximal capacity to maintain a sleep efficiency of 90% is around 8 h. Thus, episodes of more than 16 h of wakefulness lead to more consolidated and longer sleep episodes and vice versa (i.e., homeostasis). It is assumed that sleep is required to prevent the waking brain of “synaptic overload” or cellular stress. Indeed, a recent hypothesis argues that the homeostatic sleep process plays an important role in the regulation of cortical synaptic plasticity [10, 11]. However, while the physiological framework for the circadian timing system is rather well-known, the underlying basis for the sleep homeostatic function remains uncertain and is likely to be fairly complex.

Circadian and homeostatic aspects of sleep regulation are not independent of each other. Quantitative analyses of EEG activity have consistently shown that these two systems interact, not simply adding up [1, 12, 13]. This non-additive interaction suggests that minor changes in the circadian phase can have dramatic repercussions on sleep measures, if sleep pressure is high, and vice-versa.

In the following sections, we will address: (1) the circadian clock, its neuroanatomical framework, and how it regulates sleep; (2) the sleep homeostat and possible mechanisms that underlie this process; (3) the interaction of circadian and homeostatic control of sleep; (4) examples of this interaction, such as morning and evening types, short and long sleepers and healthy aging; (5) clinical conditions in which these processes go out of sync.

9.2 Circadian Sleep Process

9.2.1 How Does the Circadian Clock Work?

The circadian system modulates a wide array of human physiology and behavior patterns (for a review see [14]). Briefly, the master pacemaker driving circadian rhythms, the suprachiasmatic nuclei (SCN), acts as the central neural pacemaker for the generation and/or synchronization of circadian rhythms [15, 16]. These circadian rhythms are self-sustained and persist in the absence of environmental time cues with a remarkable precision and represent a cyclic process that can be described by the period, phase, and amplitude of the oscillation, together with its resetting sensitivity to various circadian synchronizers [4]. Under normal conditions, circadian rhythms are entrained to the 24-h day, thus enabling that behavioral, physiologic, and genetic rhythms are aptly timed with the daily changes in the environment. In order to obtain the circadian entrainment, the SCN, is synchronized to the external light–dark cycle through retinal light input (light being the main synchronizer or

“zeitgeber”) [17]. A specialized nonvisual retinohypothalamic tract provides a direct neuronal connection to the SCN from novel photoreceptors in the retinal ganglion cells that measure luminance [18, 19]. Thus, a daily resetting of the circadian pacemaker is necessary in such a manner that the imposed period of the environmental synchronizer, like the 24-h day, corresponds to the intrinsic period of the circadian oscillator, therefore ensuring a stable entrainment.

9.2.1.1 What Are the Neuroanatomical Underpinnings of the Circadian Pacemaker?

Figure 9.1 schematically illustrates the structural inputs and some of the behavioral and neuroendocrine outputs of the circadian timing system [20]. The key input and structure for entrainment of the mammalian circadian pacemaker is the eye. This is clearly demonstrated when the optic nerve is damaged, which results in loss of

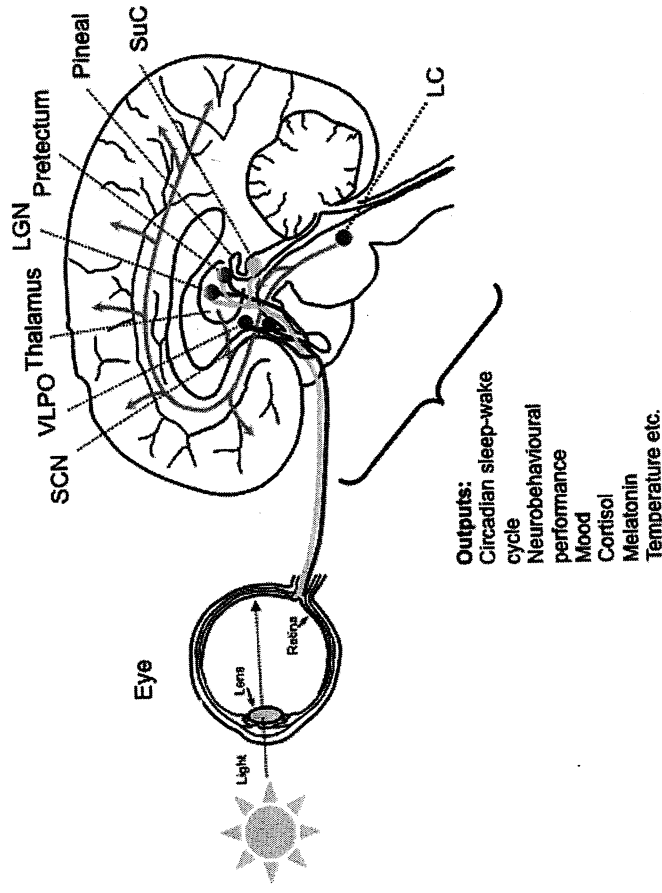


Fig. 9.1 Structural inputs and behavioral and neuroendocrine outputs of the circadian timing system. Light activates melanopsin-containing intrinsically photosensitive retinal ganglion cells and rod and cone classical ganglion cells. Melanopsin-containing ganglion cells (dark blue) project to several nonvisual areas of the brain, including the suprachiasmatic nuclei (SCN), which project multisynaptically to the pineal gland and to other areas that share input from the visual photoreceptor system (dark yellow), like the lateral geniculate nucleus (LGN), pretectum and superior colliculus (SuC). Light stimulates the ascending arousal system and eventually the cortex to optimize alertness and cognition. Moreover, light information also reaches sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO) and the noradrenergic locus coeruleus (LC) system, which is involved in the circadian regulation of arousal (modified from [165] Cajochen 2007)

entrainment, as observed in free-running rhythms in enucleated blind individuals [21]. Thus, the entrainment process involves both photoreception and central visual projection from the retina to the SCN. Initially, it was postulated that conventional photoreceptor-mediated function was essential for entrainment. However, in transgenic mice, a knockout of genes for both rods and cones does not affect entrainment [22]. It is far more probable that this process is mediated by a set of ganglion cells that contain photopigments, particularly melanopsin [19, 23]. The entrainment pathway consists in a direct projection from the retina to the SCN by the retinohypothalamic tract [24]. Furthermore, there is an important secondary visual pathway that projects to the SCN from the intergeniculate leaflets, a ventral thalamic component of the lateral geniculate complex. This pathway, the geniculohypothalamic tract, contains GABA [3] and appears to modulate the effect of the retinal input on the SCN. Furthermore, the intergeniculate leaflets obtain additional information from structures like the dorsal raphe nuclei [25]. This indicates that this path allows the tight regulation of photic and nonphotic (serotonergic pathway from the raphe nuclei) entrainment of the circadian clock.

The main circadian pacemaker is the SCN for four fundamental reasons: the SCN is where the entrainment pathway ends [3]; SCN lesions can disrupt the temporal pattern of the sleep-wake cycle and core body temperature [26]; if the SCN is isolated, it may not interfere with the SCN rhythmicity, although it certainly abolishes the sleep-wake cycle [27]; isolated SCN neurons preserve the circadian control of their firing rate [15]. The SCN is comprised of individual neuronal oscillators that form a group of pacemakers and consists of two major anatomical subdivisions, shell and core [17]. The core localizes above the optic chiasm, comprises vasoactive intestinal polypeptide-producing neurons, and receives RHT inputs, whereas the shell surrounds the core, comprises vasopressin-producing neurons, and receives hypothalamus, brainstem, and basal forebrain inputs. It is the conjunction of these subdivisions that generate the overt circadian expression of the SCN.

The SCN innervates several brain areas mostly located within the thalamus and the hypothalamus. The SCN has indirect projections via the dorsomedial hypothalamus (DMH) to the ventrolateral preoptic nucleus of the hypothalamus (VLPO) and to arousal-promoting cell groups [28]. Recently, it has been described that the VLPO, together with the wake-maintaining posterior lateral hypothalamus, can generate a "flip-flop" switch for sleep-wake control [29]. According to this model, monoaminergic nuclei, such as the histaminergic tuberomammillary neurons (TMN), locus coeruleus (LC) and the serotonergic dorsal and median raphe nuclei (DR) promote wakefulness by direct excitatory effects on the cortex and by inhibition of sleep promoting neurons of the VLPO. With an increasing reduction of the circadian drive for arousal in the later part of the waking period, there is a substantial increase in the neuron firing rate of VLPO, which is comprised of GABA neurons that project to wake-promoting areas. During sleep, the VLPO inhibits the monoaminergic-mediated arousal regions through GABAergic and galanergic projections. This leads to a progressive synchronization in the thalamo-cortical network through a synchronous discharge of the thalamic reticular nucleus [29, 30]. As a result, this strongly enhances the generation of sleep spindles and deeper

stages of NREM sleep [31]. Intermediate states between sleep and wakefulness are, thus, avoided through the reciprocal inhibition of VLPO neurons and monoaminergic cell groups, which reinforce their own firing rates in a parallel manner.

The overt importance of the "flip-flop" system can be provided by the ablation of VLPO, which results in prolonged episodes of wakefulness [29, 30]. Similarly, orexin/hypocretin, hypothalamic peptides that play an important role in maintaining wakefulness, is under the direct control of the SCN [32, 33] and has peak levels of activity at the same time of the circadian alertness signal [34, 35]. Reduced levels of these peptides can lead to the very well-known sleep attacks that occur in narcolepsy [36]. The SCN must also influence the "flip-flop" switch to produce the extended sleep-wake phases [37]. The circadian influence may be strengthened by the presence of SCN outputs by either simultaneously pressing down on one side of the "flip-flop" switch, while pushing up on the other, or sequentially pressing down or pushing up on one side, and then switching to the other side, thus regulating when sleep or wakefulness should occur.

The clock output is not only assured by neuronal projections but also involves the pituitary gland and the autonomic nervous system [28]. A classical example of the association between the SCN and the physiological responses that undergo its regulation is the secretion of melatonin by the pineal gland [38]. Melatonin is synthesized in a circadian fashion, in which maximum levels are secreted at night, with the onset of production in the later part of the day, while the lowest levels occur during the day. The increase in melatonin secretion leads to an inhibition of the firing rate of the SCN neurons, with a subsequent decline of the circadian force for arousal, thus enhancing sleep [28].

9.2.1.2 Hands of the Circadian Clock in Humans

On a behavioral level, clock outputs can be assessed by measuring rhythms, such as the circadian rhythm of core body temperature, plasma melatonin or cortisol concentration, etc. These variables, when assessed under conditions in which the confounding effects of variations in behavior and environment are controlled for, represent the "classical" markers of circadian phase, period and amplitude, which comprise parameters of "internal time" [39, 40].

9.2.1.3 Does the SCN Play an Exclusive Role as a Circadian Pacemaker?

There is a current change of opinion about the classical view of a unique circadian pacemaker orchestrating all physiological and behavioral rhythms [6]. In its place, the novel conception is that the SCN synchronizes numerous peripheral oscillators in order to achieve temporally coordinated physiology, through neural and endocrine control mediated by continuous synchronization of the SCN. In fact, neuronal signals emitted from the SCN are essential for the long-term maintenance of circadian gene expression in the periphery [41]. Thus, peripheral clocks appear to adjust

their phase and period length according to the rhythm imposed by the SCN [6]. Furthermore, these peripheral oscillators may be connected among themselves and feedback to the SCN by means of auto-regulatory feedback loops [15, 42]. How these peripheral oscillators impact on human circadian sleep-wake rhythms is not yet known. Taken together, this implies a web of pacemakers that regulates the circadian rhythms.

9.2.1.4 How Does the Circadian Timing System Modulate Sleep?

The sleep/wake cycle is perhaps the most obvious expression of the circadian rhythms in humans and the timing of this sleep/wake cycle is assumed to reflect the output of the circadian pacemaker [1]. A hallmark of this circadian regulation is the peak of REM sleep during the early hours of the morning. Within a causal framework, this peak of REM sleep may represent a circadian sleep-promoting signal to ensure the normal sleep duration. The circadian activation of REM sleep may occur by indirect projections from the SCN to the mesopontine tegmental nuclei, directly implicated with REM sleep generation [43].

Interestingly, even though the SCN plays a major role in sleep regulation, it has rather limited monosynaptic outputs to sleep-regulatory centers, like VLPO and the lateral hypothalamus [44]. Therefore, the circadian sleep regulation might be mediated by multisynaptic projections from the SCN to sleep-wake centers, such as the subparaventricular zone and the dorsomedial hypothalamic nucleus [45]. The latter, for instance, sends an intense GABAergic projection to the VLPO, thus ensuring a putative mechanism for the circadian sleep regulation [46].

However, sleep propensity depends not only on the circadian rhythmicity, but also on sleep satiety or sleep pressure, as indexed by the level of homeostatic sleep drive [47, 48]. Acute sleep loss, sleep interruptions, sleep disorders, and chronic under-sleeping dramatically increase the homeostatic sleep pressure, which, in turn, increases sleep propensity and impairs neurobehavioral performance [49, 50]. For instance, when sleep propensity is elevated, attention failures increase, irrespective of whether this is a result of acute sleep deprivation, chronic sleep loss or indeed a misalignment of circadian phase [51].

This leads to the following question: what is the role of the sleep/wake homeostat?

9.3 Sleep/Wake Homeostatic Process

9.3.1 Overview

Sleep homeostasis implies the enhancement of sleep propensity when sleep is curtailed, and its reduction when there is an excess of sleep [1, 2]. This is clearly demonstrated in sleep deprivation protocols utilized to challenge homeostatic sleep mechanisms [52–55]. Accordingly, as elapsed time awake during sleep deprivation

is extended, the increase in sleep pressure augments low-frequency EEG activity in the range of 0.75–8 Hz during NREM sleep and similarly during REM sleep. This increase can be reversed by short nap episodes, by which the high sleep pressure is therefore attenuated [56, 57]. When considering the topographical distribution of EEG activity, the homeostatic increase in low-EEG components appears to be more prominent in frontal brain areas during sleep [54, 58, 59]. Likewise, EEG activity in the sleep spindle range during NREM sleep (12–15 Hz) is modified with increased sleep pressure, in such a manner that high spindle frequency activity (>13.5 Hz) decreases, while low spindle activity (<13.5 Hz) increases [60]. Taken together, quantitative EEG analyzes in sleep deprivation protocols show that the low EEG components during both NREM and REM sleep, together with sleep-spindle activity in NREM sleep, are particularly sensitive to changes in the duration of prior wakefulness and sleep. This, in turn, implies that these specific frequency activities can act as correlates of the homeostatic sleep process. Another point to be addressed is that the decay rate of the homeostatic pressure during sleep appears to be dependent on the sleep stage. In other words, a faster decay rate happens during slow-wave sleep rather than during REM sleep [61].

While the neuroanatomical and molecular substrates for the circadian sleep regulation are rather well-known, there remains controversy concerning the potential neuronal structures responsible for sleep homeostasis [40]. Thus in Sect. 9.3.2, possible physiological underpinnings for the sleep homeostat are summarized.

9.3.2 How Does Sleep Homeostasis Occur?

Within a molecular framework, the adenosinergic system can be implicated with the sleep homeostat [62–64]. During wakefulness, increased metabolic and neural activity leads to higher extra-cellular adenosine concentrations, whereas, during sleep, there is a substantial decline in adenosine concentrations. This suggests that adenosine may be related to sleep regulation by inhibition of neuronal activity. Similarly, in humans, a genetic variant of adenosine deaminase, which is associated with the reduced metabolism of adenosine to inosine, particularly enhances slow-wave sleep and slow-wave activity during sleep [62]. Taken together, the adenosinergic system can contribute to the inter-individual variability in sleep homeostasis regulation.

The neuroanatomical underpinnings for the sleep homeostatic process are still fairly unknown. Converging lines of evidence support that local adenosine levels rise in certain cortical areas during waking and decline during sleep [65, 66]. Given that these changes are more likely to be predominant in the basal forebrain in detriment to the other cortical regions [67], local release of adenosine in this structure has been proposed as a signal for the homeostatic regulation of NREM sleep (for a review see [68]). Alternatively, electrophysiological data indicate that adenosine may disinhibit and/or actively induce sleep-promoting neurons in the VLPO area of the hypothalamus [69, 70]. Furthermore, adenosine may contribute to global cortical inhibition, due to reduced activating input from ascending cholinergic and

monoaminergic pathways and as a result of long-lasting hyperpolarizing potentials during NREM sleep [71], which consists in a type of inhibition due to a reduced activating input from the ascending cholinergic and monoaminergic pathways.

Intriguing evidence has shown that genetic processes influence the liability to sleep loss at transcriptional level, as observed in the cortical levels of Homer1a expression that strongly reflect the response to sleep loss [72]. Accordingly, the time-course gene expression analysis indicated that while more than 2,000 cortical transcripts undergo circadian control, less than 400 continue rhythmic during the course of sleep deprivation. This indicates that most diurnal gene transcription changes are sturdily dependent on the sleep/wake homeostat. Moreover, after sleep deprivation, Homer1a and three other genes – Prgs2, Jph3, and Npx2 – are over-expressed, all of which are known to play a pivotal role in recovery from glutamate-induced neuronal hyperactivity. The activation of Homer1a points towards a functional role for sleep in intracellular calcium homeostasis, which, in turn, provides a protective and recovering effect for the neuronal activation during wakefulness.

9.3.2.1 The Functional Role of the Sleep/Wake Homeostat

Recently, an interesting hypothesis – the synaptic homeostasis hypothesis – argues that sleep plays a key role in the regulation of cortical synaptic plasticity [10, 11]. A schematic diagram of this hypothesis is represented in Fig. 9.2. The novel aspect concerning this hypothesis is that, besides the proposed association between the homeostatic process and synaptic strength, it tries to unravel the specific mechanisms for this relationship. Accordingly, this hypothesis claims that wakefulness encompasses synaptic potentiation in several cortical circuits, that synaptic potentiation is intertwined to the homeostatic regulation of slow-wave activity, which, in turn, is associated with synaptic downscaling. As a result, this downscaling can relate to the beneficial effects of sleep on neural function.

Process S [9] describes the process of synaptic homeostasis, mainly by reflecting how the amount of synaptic strength in the cortex modifies due to wakefulness and sleep [10, 11]. Under normal sleep-wake conditions, synaptic strength increases during wakefulness and peaks prior to sleep, while during the sleep episode it substantially decreases until it reaches a baseline level when sleep ends. During wakefulness, the neuromodulatory setting, such as the high levels of noradrenaline, favors information storage, namely by long-term potentiation of synaptic strength. This potentiation starts when the firing of a presynaptic neuron is followed by the depolarization or firing of a postsynaptic neuron. As a result of the net increase in synaptic strength, waking plasticity progressively saturates several domains, such as learning.

On the other hand, during sleep, slow oscillations are triggered in membrane potential, which comprise the depolarized and hyperpolarized phases that enable synaptic activity to not be followed by synaptic potentiation. Furthermore, stronger cortico-cortical connections increase the degree of synchronization among populations of neurons, which reflect in slow waves of larger amplitude, particularly during the initial sleep stage [73–76]. Similarly, this may also explain why the increase in

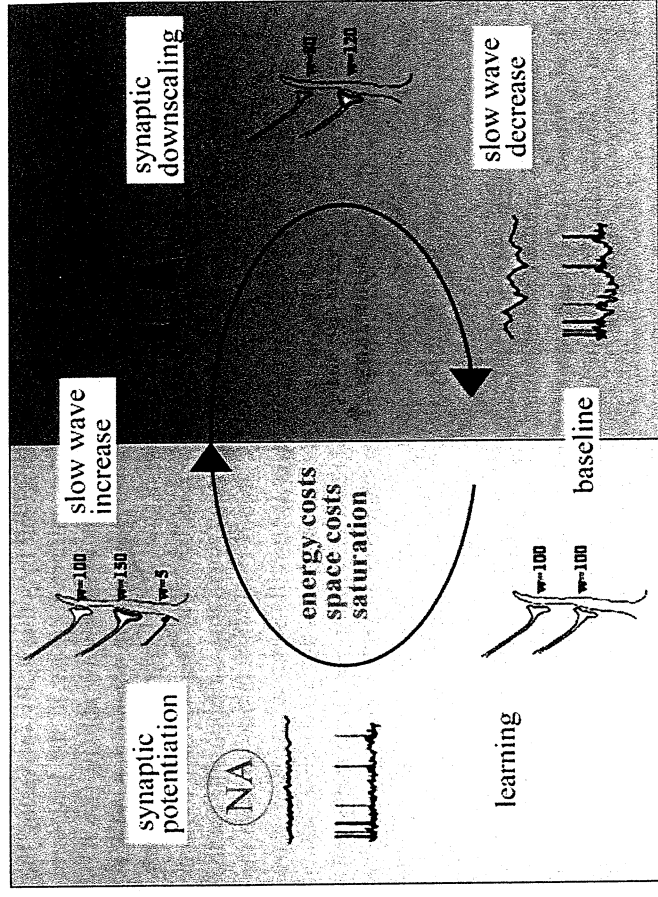


Fig. 9.2 The synaptic homeostasis hypothesis – During wakefulness (yellow background), the neuromodulatory milieu favors the storage of information, through long-term potentiation of synaptic strength (in red). Due to the net increase in synaptic strength, waking plasticity has a cost in terms of energy requirements, space requirements, and progressively saturates learning capacity. During sleep (blue background), changes in the neuromodulatory milieu trigger the occurrence of slow oscillations in membrane potential, comprising depolarized and hyperpolarized phases, which affect every neuron in the cortex, and which are reflected in the EEG as SWA (With permission from [10])

EEG spectral power density after wakefulness extends to other frequency bands besides the slow-wave or delta band [54, 77–79], although it remains to be explained why the time course of the increase varies for different frequency bands [80]. The repeated sequences of depolarization – hyperpolarization can result in the downscaling of the synapses impinging on each neuron, which implies decrease in synaptic strength. This reduced synaptic strength leads to a decrease in the amplitude and synchronization of the slow oscillations in the membrane potential [10, 11]. As a consequence, slow-wave activity progressively decreases during the rest of the sleep episode. With the attenuation of slow-waves, downscaling is gradually reduced till synaptic strength reaches a suitable baseline level. By returning synaptic plasticity to an adequate baseline level, sleep enforces synaptic homeostasis. The main advantage is that the neural circuits keep track of previous experiences, although they remain efficient at a recalibrated level of synaptic strength, which, in turn, enables the restarting of this entire process on the following waking episode.

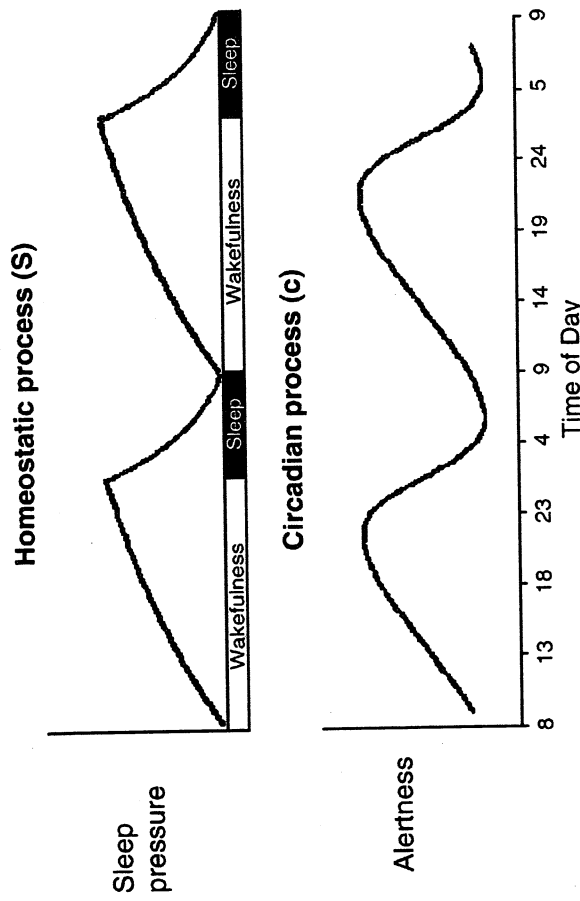


Fig. 9.3 Interaction of process *S* and process *C* – The homeostatic sleep pressure builds up during wakefulness and dissipates exponentially during sleep. The circadian process is related to the time of day, irrespective of previous sleep duration, and opposes the homeostatic process (modified from [9])

that, in addition to this system, the circadian system is equally involved in sleep regulation [90]. Indeed it is the combination of these two oscillatory processes with very different properties that best explained the timing of human sleep/wake behavior in humans living in the absence of time cues [91].

Given this important interface, the circadian and sleep homeostatic processes have been conceptualized in the two process model of sleep regulation to better understand the timing and architecture of sleep [9, 92]. According to this model, as illustrated in Fig. 9.3, the homeostatic sleep drive accumulates with each waking hour and is dissipated by sleep itself on an exponential manner. This process has properties very different from those of the circadian oscillator, which opposes the increasing homeostatic drive for sleep that builds near the end of the habitual wake day [93]. A similar process may happen during the end of the sleep episode, when sleep pressure has dramatically decreased. In order to counteract a possible arousal during these early morning hours, the circadian oscillator probably ticks in through a sleep-promoting signal, which opposes this decrease in the homeostatic sleep pressure, thus ensuring a longer sleep.

Figure 9.4 summarizes how sleep–wake cycles are regulated by circadian and homeostatic factors. Examples of this interaction can be drawn from daily variations in measures, such as alertness and neurobehavioral performance that reflect the

There is consistent evidence for this intriguing hypothesis. By increasing the total duration of wakefulness, there is a concomitant increase in the long-term potentiation related genes, followed by an increase in slow-wave activity [81–83]. Accordingly, if wakefulness is not accompanied by long-term potentiation changes in synaptic strength, the homeostatic increase in slow-wave sleep can be eliminated. Thus, it is likely that it is not wakefulness *per se*, but rather the induction of long-term potentiation molecules associated with wakefulness that is responsible for the homeostatic increase in slow-wave activity. Another evidence builds-up from the fact that, if synaptic potentiation is stronger in specific brain areas, slow-wave activity during subsequent sleep increases substantially in that given area, which suggests that sleep may be locally regulated [84–87]. This may imply that the well-known topographic differences in slow-wave homeostasis, with a predominance for frontal regions to exhibit a stronger response to sleep deprivation [54, 58, 59], can be associated to topographical differences in the susceptibility to plastic changes [88].

There are several reasons as to why sleep might be necessary for synaptic homeostasis. Perhaps the most important is that the neuronal network has to assess the total synaptic input independent of behavioral needs, in order to determine the amount of downscaling for synaptic homeostasis [10, 11]. Contrary to wakefulness, neural activity during sleep is spontaneous and happens almost detached from behavioral needs. As a result, the neuronal network can downscale appropriately. Another point is that downscaling is basically promoted by repetitive depolarization – hyperpolarization sequences, which are compatible with sleep, but would interfere with behavioral needs if it had to happen during wakefulness. Taken together, it might be that sleep plays a pivotal role for plasticity, through the homeostatic regulation of the synaptic plasticity of neuronal networks.

As illustrated in these sections, both the circadian clock and the sleep homeostatic are essential for sleep regulation. However, are these aspects of sleep regulation really independent of each other? A large body of evidence argues against this concept. In Sect. 9.4, the interplay of these two systems will be described and how both these systems contribute to the regulatory mechanisms that underlie sleep.

9.4 Circadian and Homeostatic Processes: Is It Really a Tug of War?

9.4.1 The Two-Process Model of Sleep Regulation

As illustrated in the previous sections, despite the usual controversy regarding whether it is the circadian or the homeostatic process that really underpins sleep, there is mounting evidence in support of the interaction of these two systems for sleep regulation [1, 89]. In fact, the homeostatic sleep–wake regulation cannot exclusively account for changes in sleep propensity, which leads to the assumption

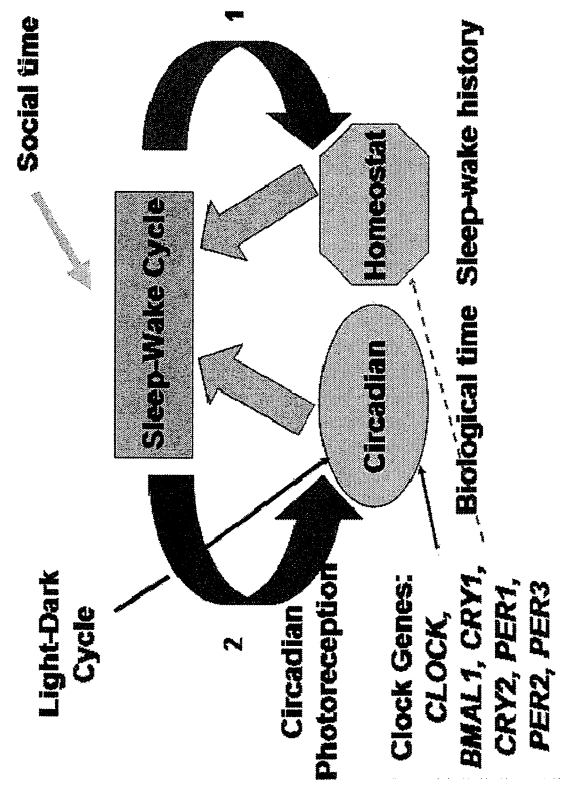


Fig. 9.4 Sleep-wake cycles are regulated by circadian and homeostatic factors – The circadian pacemaker and the sleep homeostat modulate the timing and structure of the human sleep-wake. The oscillation of the sleep homeostat is strongly determined by the sleep-wake cycle (arrow 1). Light input to the circadian clock is mediated by circadian photoreception and the sleep-wake cycle is a major determinant of this light input (arrow 2). Furthermore, social time and clock genes can underlie this process (modified from [132])

output of the circadian pacemaker in humans [47, 94, 95]. Drowsiness and attention are, respectively, increased and impaired immediately after core body temperature nadir, postulated to be near regular wake-time, the opposite being true when these measures are performed before the time at which subjects would normally sleep, as illustrated in Fig. 9.5 [94]. Paradoxically, the circadian drive for wakefulness peaks before habitual bedtime in humans entrained to the 24-h day. This contradictory phase relationship between the timing of the circadian sleep propensity rhythm and the timing of sleep and wakefulness during entrainment to the 24-h day is postulated to assist the consolidation of sleep and wakefulness in humans [96]. The circadian pacemaker opposes this increasing drive for sleep in the early evening by increasing the drive for wakefulness. Similarly, some hours prior to bedtime, the sleep promoting hormone melatonin is released in higher levels and, afterwards, melatonin receptors in the SCN suppress the firing of the SCN neurons [97]. It is possible that melatonin may serve to reduce the wake-promoting signal from the SCN, thereby promoting sleep immediately after the peak of the circadian drive for wakefulness [98]. In turn, the SCN actively promotes sleep prior to the habitual wake time, when homeostatic sleep pressure is at the lowest levels. This can be illustrated by the fact that the peak in the circadian rhythm of REM sleep happens prior to [99].

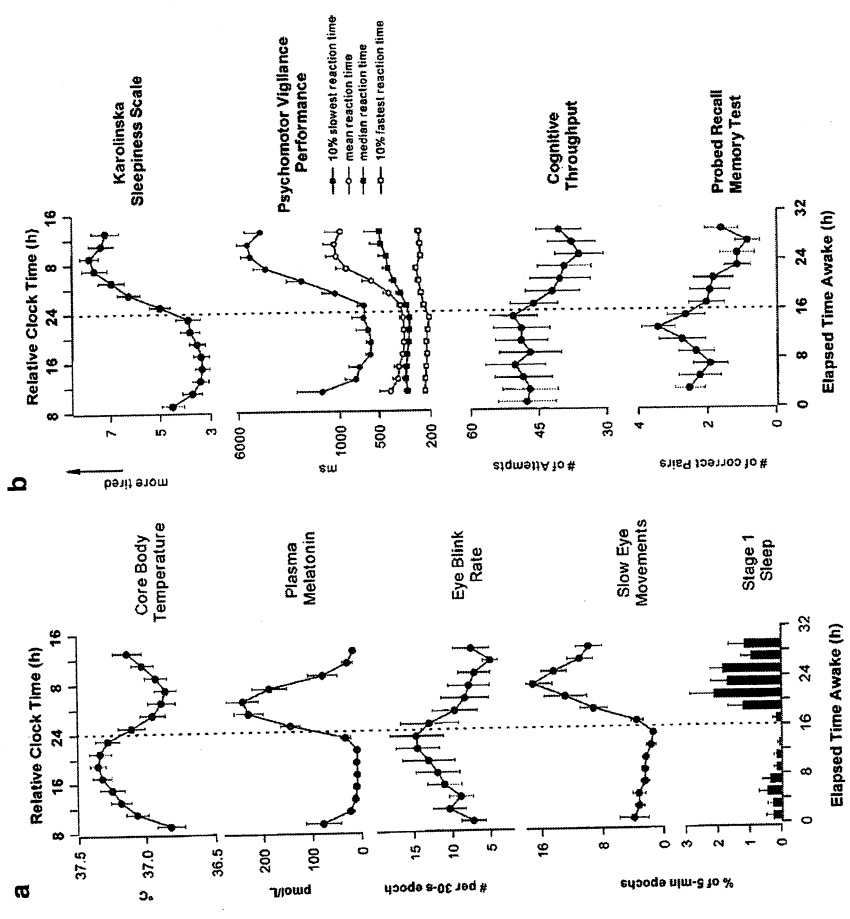


Fig. 9.5 Interaction of the circadian oscillator and the sleep homeostat – Left panel (a) depicts the time courses of core body temperature, endogenous plasma melatonin, mean eye blink rate per 30-s epoch during Karolinska drowsiness test, incidence of slow eye movements (SEMs), percentage of 30-s epochs containing at least 1 SEM/5-min interval, and incidence of stage 1 sleep (percentage of 30-s epochs containing at least 15 s of stage 1 sleep per 5-min interval) are shown, averaged across ten subjects \pm SE. Right panel (b) illustrates the time course of subjective sleepiness as assessed on Karolinska sleepiness scale (KSS; highest possible score = 9, lowest possible score = 1), psychomotor vigilance performance [mean, median, 10% slowest and fastest reaction times in ms (logarithmic scale)], cognitive performance (numbers of attempts in 4-min two-digit addition task), and memory performance (number of correct word pairs in probed recall memory task) are shown averaged across ten subjects \pm SE. All data were binned in 2-h intervals and expressed with respect to elapsed time since scheduled wake-time. Vertical reference line indicates transition of subjects' habitual wake- and bedtime (with permission from [94])

9.4.2 Are These Two Systems Independent or Complementary?

How the circadian and the homeostatic process interact is still a matter of intense debate. For instance, it is not yet clear where in the central nervous system this possible interaction occurs and whether the SCN directly or indirectly interacts

with the brain centers responsible for the sleep homeostatic process, such as the basal forebrain and the VLPO. Prior studies focusing on SCN-lesioned animals provide evidence that the homeostatic process is still operative and is not drastically changed [93, 100]. This argues in favor of the two processes being probably independent from each other. On the other hand, it might be that the circadian and the homeostatic processes interact more downstream in the cascade or that the output variables of measurement do not reflect an accurate interaction [13, 101].

In rats, the combination of SCN neuronal activity with EEG recordings revealed that changes in vigilance states are paralleled by strong variations in SCN activity [102]. During REM sleep, SCN activity was elevated, whereas in NREM sleep it was substantially decreased. In concomitance, two types of sleep deprivation – of slow-wave sleep in NREM and of total REM sleep – were carried out to prove that variations in SCN activity are related to changes in vigilance state [102]. Accordingly, SCN activity appeared to be differentially affected by the alternations of sleep states and these sleep-dependent changes were superimposed on the circadian modulation in SCN activity. Given that the SCN neuronal activity was tightly correlated to fluctuations in slow-wave activity, it is likely that the SCN receives continuous input about changes in sleep homeostasis.

To conclusively illustrate in humans how these processes interact and in order to quantify their strength in the control of sleep and wakefulness, protocols must be applied to disentangle these two processes [2]. Why? The sleep–wake cycle can be usually observed directly. The challenge, though, has been to separate the relative contribution of the sleep homeostat, the circadian clock and the light input to sleep–wake characteristics. Such an assessment mostly requires controlled laboratory conditions, since in the daily world the timing of this sleep–wake cycle is strongly modulated by our social demands and artificial lighting environments.

9.4.2.1 What Can Happen When One Disentangles These Two Systems?

Devoid of the imposed light–dark and social cycles, sleep remains consolidated, although it desynchronizes from the 24-h solar day. In concomitance, one observes dramatic changes in the internal phase relationship between core body temperature and the sleep–wake cycle [103]. For instance, sleep can initiate near the core body temperature nadir, instead of 6 h before. This drastic change in the phase relationship suggests that some distinguished oscillators rule these rhythms. A thrilling example is the spontaneous internal desynchrony [104, 105]. Under this free-running condition, subjects live in an environment free of time cues and self-select the light–dark cycle to which they are exposed. The sleep–wake cycle then oscillates with a longer or shorter period when compared with the other physiological measures, although the period of core body temperature rhythm remains rather stable. Accordingly, the longest spontaneous sleep duration habitually occurs when sleep starts near to the wake-maintenance zone and at the peak of the core body tempera-

ture [106–108]. Similarly, the crest of the REM sleep propensity rhythm is situated close to core body temperature nadir [106–108]. As a consequence, sleep is initiated on a broader range of circadian phases. Under such conditions, waking activities, such as food intake and hourly time estimation, are associated with the sleep–wake cycle period and perhaps are not ruled by the circadian pacemaker.

In the forced desynchrony protocol (FD), participants live on artificially either very long or very short days [39]. This imposed desynchrony between the sleep–wake schedule and the output of the circadian pacemaker occurs only under conditions in which the sleep–wake schedule is outside the range of human entrainment. As a consequence, the circadian system cannot be entrained to the new imposed sleep–wake cycle. Accordingly, scheduled sleep and wake episodes happen at nearly all circadian phases, and when light intensity during scheduled waking episodes is kept low, the pacemaker can free-run with a stable period in the range of 23.9–24.5 h [4]. Since subjects are scheduled to stay in bed in darkness, the variation in the amount of wakefulness prior to each sleep episode is significantly minimized. This enables to average data either over successive circadian cycles or over successive sleep or wake episodes, therefore separating the circadian profile of a given variable by removing the confounding sleep–wake-dependent contribution or vice versa.

A wide array of interactions between the sleep–wake cycle and circadian processes in the regulation of sleep, the EEG during sleep and wakefulness, alertness, motivation, and neurobehavioral and physiological variables can be unraveled through this protocol [12, 90, 109–111]. For example, forced desynchrony studies have revealed that sleep efficiency is maximum when subjects sleep at the circadian phase during which endogenous melatonin is released [112]. In contrast, wakefulness during the sleep episode is highest when sleep is scheduled to happen at a circadian phase during which endogenous melatonin secretion is absent [112]. This led to the hypothesis that melatonin administration may improve sleep efficiency at such times, which in fact happened when melatonin was administered 30 minutes prior to scheduled sleep, leading subjects to experience 30 minutes of more sleep when they slept at a circadian phase without the release of endogenous melatonin [113]. Contrariwise, there was no effect of melatonin administration on sleep efficiency and sleep duration when melatonin was administered at the circadian phase of endogenous melatonin production. Thus, melatonin efficacy appears to be dependent on the circadian phase and serves as an interesting example as to how strongly the circadian and homeostatic mechanisms underpinning sleep are intertwined.

Taken together, quantitative analyzes of the interaction between these two systems provide strong evidence that these two factors interact, and not merely add up [1, 2], as illustrated in Fig. 9.6 ([166]). This implies that the amplitude of the circadian modulation of sleep depends on homeostatic sleep pressure [110]. As an illustration, when sleep pressure is low the circadian variation in performance is equally small. Similarly, as will be depicted in Sect. 9.4.3, changes in circadian amplitude together with variations in sleep pressure may happen for sleep spindle activity, REM density, sleep consolidation and so forth. This non-additive nature implies that relatively slight variations in the circadian phase can have major repercussions on a given variable, if

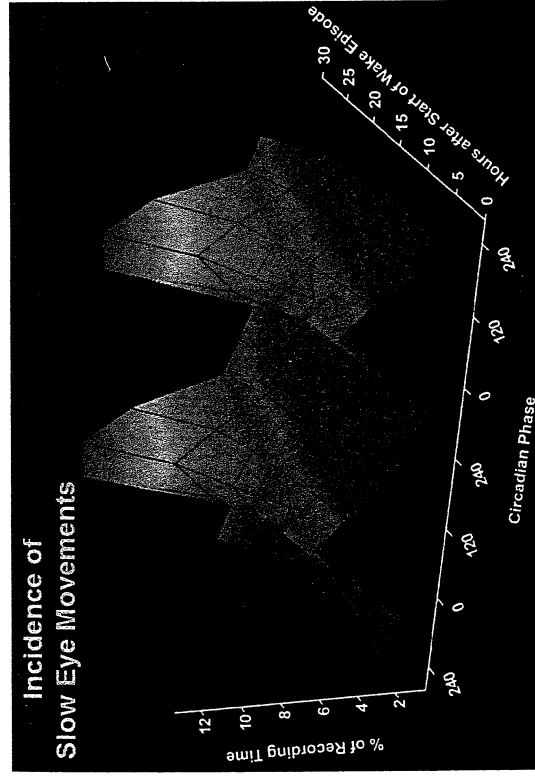


Fig. 9.6 Non-additive nature of the circadian oscillator and the sleep homeostat – Incidence of slow eye movements expressed in terms of percentage (%) of recording time (z-axis) and hours after start of sleep episode (x-axis) in relation to the circadian phase (x-axis, 0 indicating core body temperature nadir) (with permission from [166])

sleep pressure is high, the contrary also being true. In Sect. 9.4.3, we will summarize the possible homeostatic and circadian influences on the sleep EEG.

9.4.3 What is Homeostatic and/or Circadian in the Sleep EEG Activity?

The circadian and the homeostatic processes play a multitude of roles during sleep. An indication about the strength of these processes on EEG activity builds up from previous FD studies, in which the period of the sleep–wake cycle was either 28 or 42.85 h [4, 110]. Accordingly, the circadian rhythm of endogenous melatonin oscillated within a 24-h basis and with a similar period of the circadian rhythm of core body temperature, thus leading to a desynchronization of these rhythms [2, 12]. EEG power spectra during wakefulness, REM sleep and NREM indicated high alpha power during wakefulness, predominance of low frequencies and in the spindle range during NREM sleep, and lower values in the same frequency bins during REM sleep. This suggests that the relative contribution of the circadian and homeostatic processes exhibited frequency-specific modulation. During all stages of vigilance, low EEG components were predominantly modulated by the homeostatic factor. On the other hand, the circadian modulation of the EEG differed across these states, such that the maximum circadian variance was shown for REM sleep in the alpha activity range and for NREM

sleep in the low spindle frequency activity (Fig. 9.7) [112]. An interesting aspect in the EEG power spectra regards sleep spindles, which are primarily generated and modulated by a thalamocortical network, which comprises the interplay between reticular thalamic, cortical pyramidal, and thalamocortical cells [115]. Initially, the progressive hyperpolarization of thalamocortical cells after sleep onset results in the appearance of spindle oscillations, which are then replaced by slow-wave oscillations, when deepening of sleep proceeds, and thalamocortical neurons achieve a voltage range at which slow-wave oscillations are triggered [116]. Thus, sleep spindles are deemed to play a key role in neuronal plasticity and sleep maintenance, basically by inhibiting the sensory information that reaches the cerebral cortex [117].

When the sleep episode coincides with the circadian phase of endogenous melatonin secretion and when it is highly consolidated, mild reductions in the frequency range of slow-waves and theta activity are observed in the NREM sleep, while profound variations occur in the spindle frequency activity [48, 90]. Low frequency sleep spindle activity (12.25–13 Hz) exhibits an outstanding circadian modulation, with maximum levels during the circadian phase of melatonin secretion [112]. This has been interpreted as evidence for the circadian modulation of the frequency of sleep spindles.

Taken together, spectral hallmarks of EEG activity during sleep exhibit a frequency-specific homeostatic and circadian modulation. These two independent oscillatory processes correspond to an essential component of cortical activation during sleep, which is likely to be related to the processing of external sensory stimuli and behavioral responses [2].

Given the fundamental role played by these systems on the EEG activity, questions emerge: What about genes? Can the molecular machinery be implicated with the circadian and homeostatic modulation? If so, how and to what extent is its role? In Sect. 9.4.4, we will address some of the exciting ideas that are going on in this field.

9.4.4 What is the Role of Genes in the Circadian and Homeostatic SLEEP Modulation?

The molecular machinery that underlies circadian and homeostatic sleep regulation still has many gaps of uncertainty, although many of its features are being unraveled. Human circadian oscillators are considered to rely on the transcription/translation feedback loops in clock gene expression [15, 118, 119]. The molecular interplay of clock genes consists largely of clock RNA and proteins that oscillate in a circadian style, through positive and negative feedback loops of transcription and translation. The encoded protein of two core clock genes, *clock* and *bmal1*, binds as a transcription factor to the DNA. The *Clock-Bmal1*-complex translocates to the nucleus whereby it induces transcription of the other core clock genes like *per 1*, *2* and *3* and *cry 1* and *2*. *mcry1* and *2*, in turn, inhibits the transcriptional activity of *Clock* and/or *Bmal1*, thereby inhibiting their own transcription, whereas *mper2* is involved in transcription of *Bmal1*. *Per3* forms heterodimers with *Per1/2* and *Cry1/2*, respectively, and enters into the nucleus, resulting in the inhibition of *Clock-Bmal1*-mediated

transcription [120]. Furthermore, the major and crucial loop involves the autorepression of cryptochrome (Cry1, Cry2) and period (*Per1*, *Per2*) genes and this rhythm-generating circuitry is functional in most cell types [15, 118, 119].

Besides the circadian system, clock genes also affect sleep homeostasis. For instance, the mutation in mice clock gene can lead to alterations of sleep homeostasis [121, 122]. Indeed, when compared with the heterozygous or wild type, homozygous mice showed less and shorter NREM sleep episodes and significantly lower delta frequency during light-dark cycles. Similarly, mice tested on their incapacity to respond to sleep pressure by being sleep deprived for 6 h revealed that the homozygotes slept less than the heterozygotes or the wild type. Analysis of recovery night supported the concept that homozygous mice responded to sleep deficit by increasing sleep time and total amount of sleep [121].

The functional role of *mPer1* and *mPer2* genes in the homeostatic regulation of sleep has been unraveled by the comparison of mice deficient in *mPER1* – *mPer1* mutants – or in *mPER2* – *mPer2* mutants – with wild-type controls after sleep deprivation [123]. Under this condition, all mice exhibited an increase of slow-wave activity in NREM sleep, which is known to reflect the homeostatic response to sleep deprivation. Furthermore, this increase was topographically more predominant in frontal regions in relation to the occipital regions. While all genotypes did not differ with respect to the effects of sleep deprivation on the occipital EEG, the effects on the frontal EEG were initially diminished in both *mPer* mutants. Differences between the genotypes were observed during the time course of the 24-h distribution of sleep, and reflected especially the phase advance of motor activity onset in *mPer2* mutants. Whereas the daily distribution of sleep was modulated by *mPer1* and *mPer2* genes, sleep homeostasis, as indexed by the increase in slow-wave activity after sleep deprivation, was relatively preserved in the *mPer* mutants.

Another evidence in support of a non-circadian role for clock genes in sleep homeostasis buildsup from a study focused on the time course of forebrain changes in the expression of *per1* and *per2* during sleep deprivation and subsequent recovery in sleep in three inbred strains of mice [124]. Accordingly, in all mice strains *per1* and *per2* expression increased during sleep deprivation, particularly in the D2 mice strain for which the sleep rebound was lowest. Furthermore, while in the other two strains *per1* and *per2* reverted to control levels during recovery sleep, *per2* expression continued high in D2 mice. Taken together, this provides a functional role for clock genes in the homeostatic sleep regulation.

The non-circadian role of clock genes has also been described for humans. For instance, the human *period3*, one of the several clock genes, is under current extensive investigation due to its implication in the circadian regulation and sleep homeostasis.

first day of the forced desynchronization protocol, immediately upon release from entrainment. Plasma melatonin data were expressed as Z-scores to correct for inter-individual differences in mean values. REM sleep is expressed as a percentage of total sleep time (TST). Low-frequency sleep spindle activity in NREM sleep and Alfa activity in REM sleep are expressed as percentage deviation from the mean. Data are double plotted, i.e., all data plotted left from the dashed vertical line are repeated to the right of this vertical line (with permission from [112])

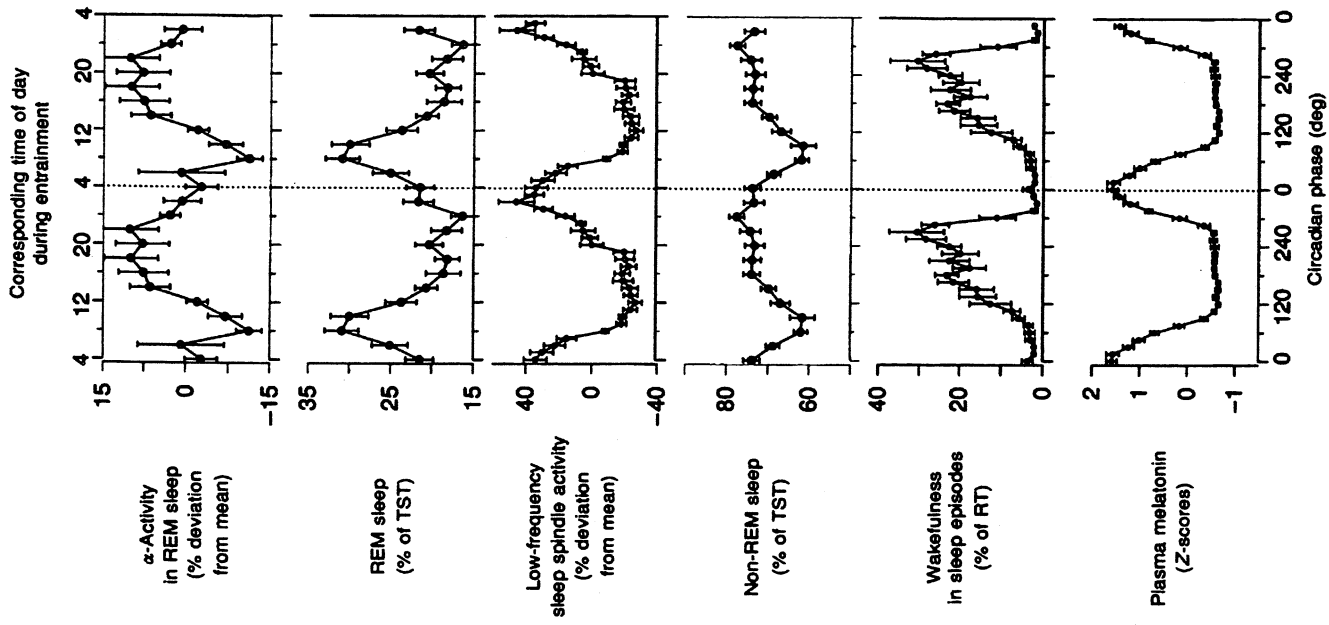


Fig. 9.7 Circadian EEG components – Phase relationships between the circadian modulation of Alfa activity in REM sleep (first panel), REM sleep (second panel), low-frequency spindle activity in NREM sleep (third panel), and plasma melatonin (last panel). All data are plotted against circadian phase of the plasma melatonin rhythm (0 deg corresponds to the fitted maximum, bottom x-axis). Top x-axis indicates the average clock time of the circadian melatonin rhythm during the

Peak levels of *PER1*, 2 and 3 are known to happen during diurnal activity time in human peripheral blood cells, with greater levels of mRNA expression approximately 9 h after the melatonin peak [125]. Furthermore, the phase of peripheral clock gene expression in leukocytes can be strongly associated with the habitual sleep timing and *PER3* expression can be correlated with melatonin and cortisol phase [126]. While considering all these three clock genes, *PER3* has been shown to be the most robust marker of the circadian gene expression, together with cortisol and melatonin. However, despite the fact that *PER3* expression can act as a marker for the entrained phase, this does not imply that it can have direct repercussions on entrained phase. It can be argued, for instance, that its effects on the diurnal preference can be mediated by the effects on the sleep-wake homeostat, and not through the timing of core circadian markers [127]. This idea is supported by a recent study focusing on the contribution of *PER3* polymorphism on sleep-wake regulation [127]. Briefly, the coding region of the *PER3* gene has a variable-number tandem-repeat polymorphism, in which a design encoding 18 amino acids is repeated either four (*PER3*⁴) or five times (*PER3*⁵), thus indicating that subjects can either be homozygous for *PER3*⁴ or *PER3*⁵ alleles or heterozygous *PER3*^{4/5} [120]. In comparison to *PER3*^{4/4} individuals, homozygosity for *PER3*⁵ had a remarkable effect on several markers of sleep homeostasis: increase in slow-wave sleep and slow-wave activity in NREM sleep (baseline night), together with an increase in theta and alpha activity in REM sleep (baseline night), as illustrated in Fig. 9.8.

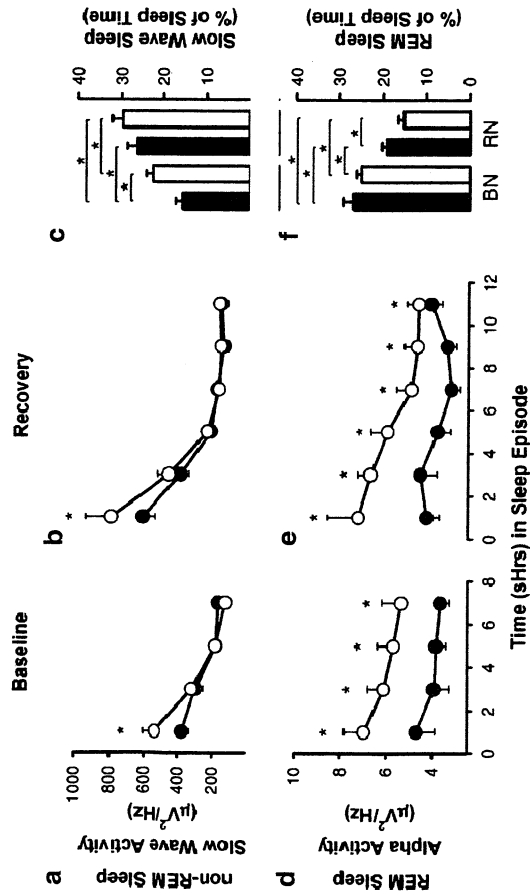


Fig. 9.8 *PER3* polymorphism and sleep structure – Dynamics of slow-wave activity in NREM Sleep, alpha activity in REM Sleep, and sleep-stage response to sleep loss differ between *PER3*^{5/5} and *PER3*^{4/4} (a, b, d, and e) Time courses of slow-wave activity in NREM sleep and alpha activity in REM sleep during baseline and recovery sleep episodes for *PER3*^{5/5} (open symbols) and *PER3*^{4/4} (filled symbols). (c) Slow-wave sleep time and (f) REM sleep time expressed as a percentage of total sleep time for baseline and recovery sleep in *PER3*^{5/5} (white bar) and *PER3*^{4/4} (black bar) (with permission from [127])

These differences in slow-wave and slow-wave activity were sustained during recovery sleep even after 40 h of sleep deprivation. Taken together, *PER3*^{5/5} individuals are likely to live under a comparatively higher sleep pressure and are more susceptible to the effects of sleep loss [127]. Interestingly, the circadian rhythms of melatonin and cortisol were not affected. In other words, the classical markers of amplitude and phase of circadian physiology are not affected by this polymorphism. Within the framework of the homeostatic and circadian regulation of sleep, these data imply that the *PER3* polymorphism appears to contribute to the differences in sleep structure by its effects on the homeostatic facet of sleep regulation. The independence of these two processes has been a mainstay of our current models of sleep regulation [128]. Nevertheless, it might be that this concept does not extend to the molecular level, and that some genes previously described as clock genes can perform the noncircadian roles.

How can one see the interaction of these two oscillatory systems in healthy people? There are three examples of natural models: the interaction of these two systems in morning and evening types, in short and long sleepers and in healthy aging. In Sect. 9.4.5, we will focus on the first model.

9.4.5 Morningsness and Eveningness: The Clock Ticks with the Homeostatic Hourglass

Morningsness–eveningness, also described as “chronotype”, comprises the individual characteristic related to the preference in sleep timing, according to which morning types habitually choose to sleep approximately 2 h earlier than the evening types [129]. An underlying hypothesis for this individual difference could be the internal circadian phase, with an earlier circadian phase in morning than in evening types [130]. However, it has been recently shown that morning and evening types have similar circadian phases [131]. Given that the homeostatic process plays a fundamental role in the regulation of sleep–wake behavior [132], one could argue that morningsness–eveningness may result from the individual differences in the homeostatic sleep regulation. In line with this assumption, recent studies have questioned whether differences in the dynamics of nocturnal homeostatic sleep pressure can underlie differences in sleep timing preference [133, 134]. In the subjects with intermediate circadian phases (Fig. 9.9), both initial level and decay rate of slow-wave activity in the frontal derivation during NREM sleep were higher in morning than in evening types. Furthermore, no correlation was elicited between slow-wave activity decay and dim light melatonin onset (DLMO). This supports the idea that chronotype can occur as a consequence of different dissipation levels of sleep pressure. All in all, it might be that, instead of “chronotype”, the expression “homeotype” coins what really happens in the morningsness and eveningness.

Recently, a fascinating study [135] using functional magnetic resonance imaging (fMRI) in extreme morning and evening types revealed that sustained attention in evening was intertwined to enhanced activity in evening than morning chronotypes

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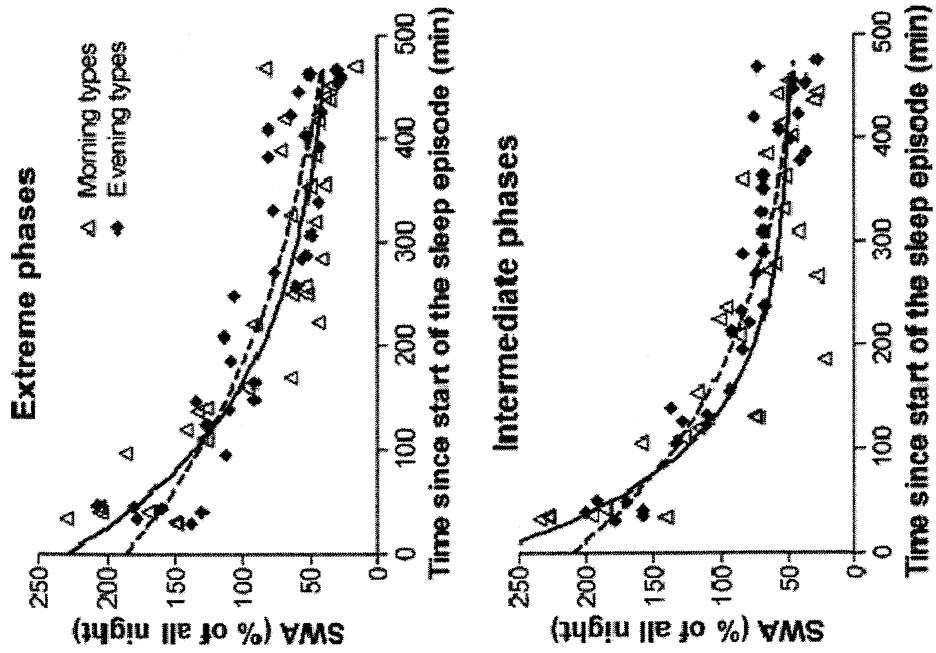


Fig. 9.9 Slow-wave activity in morningness and eveningness – Exponential decay functions adjusted on relative slow-wave activity in NREM sleep for all night EEG in frontal derivation. Solid line, morning types; dashed line, evening types. Subjects with extreme circadian phases are depicted in upper panel and subjects with intermediate circadian phases are depicted in lower panel (with permission from [134])

in the LC and in a suprachiasmatic area (SCA), both deeply involved in the circadian wake-promoting signal. In parallel, it was revealed that SCA activity was inversely related to slow-wave activity during the first NREM sleep episode. In other words, SCA activity decreases with increasing homeostatic sleep pressure, which provides strong evidence for the direct influence of the homeostatic and circadian interaction on the neural activity underpinning sleep. In Sect. 9.4.6, we focus on how these two sleep oscillators play a role in short and long sleepers.

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9 The Circadian Clock and the Homeostatic Hourglass

9.4.6 Short and Long Sleepers: How Do the Circadian Clock and the Sleep Homeostat Work?

To look at the possible differences of these two oscillatory systems in habitual short and long sleepers, parameters of the buildup and dissipation of sleep pressure, as indexed by the time course of slow-wave activity during sleep before and after 24 h of sleep deprivation, were carried out [136]. Accordingly, total sleep time was more than 3 h longer in the long sleepers than in the short sleepers. The enhancement of EEG slow-wave activity in NREM sleep after sleep deprivation was larger in long sleepers than in short sleepers. This difference in slow-wave activity was predicted by the two-process model of sleep regulation on the basis of the different sleep durations for both groups. This suggests that short sleepers live under a higher NREM sleep pressure than long sleepers, even though they do not necessarily differ with respect to sleep homeostat mechanisms. On the circadian domain, long sleepers usually exhibit longer circadian rhythms of core body temperature, melatonin and cortisol in detriment to short sleepers [137]. These differences may be attributed as either the cause or consequence of differences in sleep duration, since sleep is tightly related to the end of light input to the circadian pacemaker.

Another natural model looking at the interaction of these two systems is healthy aging. As every dynamic system, it is clear that neither the circadian modulation of sleep nor the sleep homeostat remains constant throughout one's entire lifetime. Given that, in what manner do these changes occur? Does the balance of changes tilt more towards one of these processes? Section 9.4.7 summarizes the current state-of-art about age-related changes within these two complex oscillatory systems.

9.4.7 Circadian and Homeostatic Sleep Regulation: What Happens with Age?

Advanced age implicates changes in numerous aspects of the sleep-wake cycle. Among these, evidence points towards shallower nocturnal sleep associated with increase number of arousals, a decrease in slow wave sleep and more daytime naps [138, 139]. Similarly, there appears to be attenuated amplitude of circadian markers, such as melatonin, core body temperature and cortisol [140]. Older individuals tend to present earlier sleep times with a concomitant advanced circadian phase in relation to core body temperature minimum [141, 142], although the endogenous circadian period is quite stable [4]. However, it is still a matter of debate as to whether it is the circadian or the homeostatic facet of sleep which undergoes more changes with aging. It is very likely that the sleep homeostat remains operational after sleep deprivation in older individuals [143]. On the circadian domain, although some aspects of circadian sleep regulation seem to be affected by age [144], it is unclear whether it is aging *per se* or the modified regulation of circadian signaling downstream or both that are the underlying reason for these changes [40].

in comparison to the older participants, in which it lasted solely in the first NREM sleep episode. This dataset implies that the homeostatic sleep response to low sleep pressure is rather similar in older and young subjects.

What if these two processes go out of tune? Are there any clinical implications for a mal-functioning of these processes? Section 9.5 addresses some clinical scenarios in which the circadian and/or the homeostatic processes undergo some clear disruptions.

9.5 What Happens When the Two Sleep Processes Go Out of Sinc?

Changes in the circadian pacemaker may contribute to a wide array of dysfunctions, such as mood, sleep disturbances and cognitive performance [147, 148]. Given that the circadian timing system is extremely sensitive to environmental light and melatonin, it may not function in optimal levels in the absence or decrease of their synchronizing effects. For instance, elderly patients with dementia are very likely to experience functional deficits in the circadian timing system and attenuated synchronization if light exposure and melatonin production are reduced [149]. Recently, it was investigated whether cognitive and non-cognitive symptoms associated with dementia can decrease by bright light exposure [149]. Accordingly, light substantially attenuated cognitive deterioration, depressive symptoms and the increase in functional limitations. The possible underlying reasons may be that the long-term use of bright light improves the SCN ability to synchronize rhythms in hormones, metabolism and peripheral oscillators, with further repercussions on general functioning.

Alzheimer disease (AD) is another neurological condition associated with a wide range of changes in circadian rhythms [150]. For instance, rhythmic levels of several hormones, such as cortisol, melatonin, vasopressin, pulsatile luteinizing hormone and β -endorphine, are substantially modified in AD patients [151]. A significant increase of nocturnal serum cortisol levels in AD patients appears to be associated with a disturbance of sleep-wake rhythms [152]. Furthermore, the sensitivity of the hypothalamic-pituitary-adrenal axis to the steroid feedback appears to be highly impaired. In particular, pineal melatonin secretion and pineal clock gene oscillation can be disrupted in AD patients, and, surprisingly, even in non-demented controls with the earliest signs of AD neuropathology, in contrast to non-demented controls without AD neuropathology [151]. Furthermore, a functional disruption of the SCN was described from the earliest AD stages onwards, as shown by a decreased vasopressin mRNA, a clock-controlled major output of the SCN. This functional disconnection between the SCN and the pineal gland from the earliest AD stage onwards may be responsible for the pineal clock gene and melatonin changes, which can underlie the circadian rhythm disturbances in AD.

Circadian and homeostatic disruptions can play an essential role in the pathogenesis of mood disorders, particularly in depression. Sleep disturbances in depression include

In order to unravel these questions, it was hypothesized if age-related changes in sleep can result from an attenuated circadian arousal signal during the evening. The main assumption underlying this idea is that the human circadian pacemaker notoriously maintains timing and consolidation of sleep by opposing increased homeostatic sleep pressure, particularly in the evening during the “wake maintenance zone” [40]. If the circadian signal is dampened with age, this opposition would not be so clear-cut. As one might expect, quantitative evidence for a dampened circadian arousal signal in older individuals (Fig. 9.10) was observed through an increased sleep in the wake maintenance zone [145]. Additionally, older individuals had a comparatively decreased melatonin secretion. On the EEG domain, older participants exhibited a reduction in circadian modulation of REM sleep, together with less obvious day-night differences in the alpha and spindle range of sleep, both of which clearly undergo a circadian regulation. Taken together, this implies that the age-related changes in sleep propensity can be underpinned by a reduced circadian signal opposing the homeostatic sleep drive.

While considering the sleep homeostat, there is evidence for two types of situations: (1) under high sleep pressure, older subjects exhibit an attenuated frontal predominance of sleep EEG delta activity [143]; (2) under low sleep pressure, in which sleep pressure is maintained low by intermittent 75-min naps scheduled every 150 min for 40 h under constant routine conditions, there are slight age-related differences [146]. In this case, there appears to be a significant decline of EEG power density in the delta range and an increase in the sleep spindle range during recovery sleep. Nonetheless, the delta range response to low sleep pressure was more enduring in young individuals, given that it lasted for the first two NREM sleep episodes,

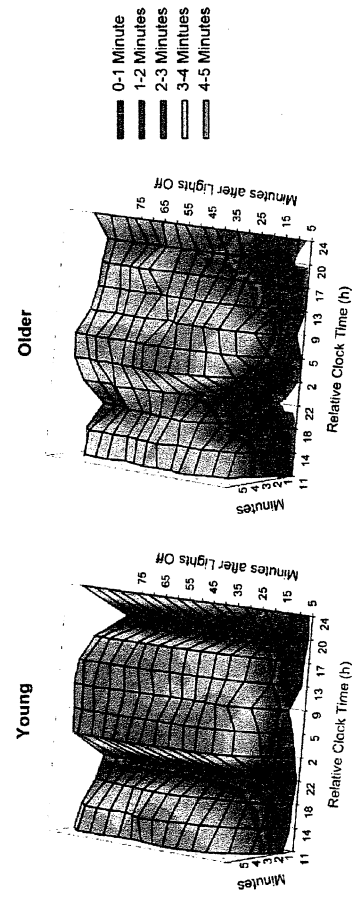


Fig. 9.10 Dampened circadian arousal signal in older individuals – Three-dimensional plots of total sleep time for young and older subjects. The x-axis represents the averaged mid-nap clock times for both age groups and the y-axis the time course within the respective naps (3–4 min). The z-axis specifies the amount of sleep per 5 min bin of each nap (min). Short-wavelength colors (blue, green) illustrate less sleep, longer wavelength colors (yellow, orange), more sleep. During the wake-maintenance zone (around 22 h – day 1 – and 20 h – day 2 – respectively) older individuals have comparatively more sleep (with permission from [145])

shortening of the REM sleep latency and an abnormal distribution of REM sleep during the night [153]. These REM sleep alterations, which exhibit a clear circadian pattern, appear to be more prominent in depressive states [154]. Abnormalities in the circadian rhythm of depressed patients may also include variations in the circadian phase and amplitude of core body temperature, with an increase in nocturnal body temperature amplitude [147, 155]. It is still unclear whether these observations represent functional changes of the circadian oscillator or are influenced by other factors. Similarly, there is some evidence in support of a decrease in nocturnal secretion of melatonin in depression [156], although this is still controversial.

Depression is habitually associated with sleep disturbances, like insomnia [157] and excessive daytime sleepiness [158, 159]. Interestingly, individuals genetically predisposed towards “eveningness” (a preference for the evening) in relation to “morningness” (a preference for the morning) are more prone to develop depression [160]. Genetic variations in the circadian genes have been found to associate with these sleep disorders and diurnal preference measures, and includes an association between certain variants of *PER1*, *PER2*, *PER3* and *Clock* [120, 161–163]. This suggests a connection between proper mood regulation and normal functioning circadian molecular machinery.

Together with the circadian system, depressed patients may also suffer a deficiency in the homeostatic buildup of sleep pressure during extended wakefulness. It is unclear whether alterations in sleep regulatory mechanisms are associated with the pathophysiology of depression, and it might be that the homeostatic facet of sleep remains functional in this clinical condition [164]. Nevertheless, in some types of depressions, such as seasonal affective disorder (SAD), patients do appear to have changes in the buildup of homeostatic sleep pressure during wakefulness, irrespective of clinical state or season [114]. It is possible that SAD patients may have a trait – rather than state – deficiency in the homeostatic build up of sleep pressure during an extended wakefulness, as indexed by subjective sleepiness and EEG theta-alpha activity.

9.6 Concluding Remarks

Day-to-day rhythms in sleep are underpinned by the interplay of the circadian clock and the sleep homeostat. Both these internal oscillators contribute in an independent and non-additive manner to numerous dimensions of sleep, such as sleep timing and duration, REM sleep, NREM sleep, and so forth. The relative contribution of these two systems cannot be predicted by either oscillator independently. Instead, they decisively depend on their phase relationship and amplitude. In other words, the amplitude of the most circadian variations in sleep crucially relies on the sleep homeostat, and vice-versa. Therefore, it is this opposing interaction between the circadian and homeostatic changes in sleep propensity that consolidates sleep. The implications of disruption in these two systems can be clearly evidenced in psychiatric and neurological disorders that are intertwined to circadian rhythms and

to the sleep homeostat on a wide array of dimensions. Knowledge on these systems may help to unravel the pathophysiology of these disorders and offer potential therapeutic strategies. The theoretical framework for both processes is under intense investigation. While several neuroanatomical pathways have been described for the circadian timing system, the mechanisms responsible for the generation of the homeostatic sleep process are still under thorough debate. New data on the genetical and molecular expression, like clock gene polymorphisms, may shed new light on the inter-individual differences associated with sleep architecture, timing and duration. This promises a fascinating future for the circadian and homeostatic sleep research.

References

1. Dijk DJ, Von Schantz M (2005) Timing and consolidation of human sleep, wakefulness, and performance by a symphony of oscillators. *J Biol Rhythms* 20:279–290
2. Cajochen C, Dijk DJ (2003) Electroencephalographic activity during wakefulness, rapid eye movement and non-rapid eye movement sleep in humans: Comparison of their circadian and homeostatic modulation. *Sleep Biol Rhythms* 1:85–95
3. Moore RY, Speh JC, Leak RK (2002) Suprachiasmatic nucleus organization. *Cell Tissue Res* 309:89–98
4. Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, Rimmer DW, Ronda JM, Silva EJ, Allan JS, Emens JS, Dijk DJ, Kronauer RE (1999) Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 284:2177–2181
5. Gachon F, Nagoshi E, Brown SA, Ripperger J, Schibler U (2004) The mammalian circadian timing system: from gene expression to physiology. *Chromosoma* 113:103–112
6. Schibler U, Sassone-Corsi P (2002) A web of circadian pacemakers. *Cell* 111:919–922
7. Hastings MH, Herzog ED (2004) Clock genes, oscillators, and cellular networks in the suprachiasmatic nuclei. *J Biol Rhythms* 19:400–413
8. Moore RY (1997) Circadian rhythms: basic neurobiology and clinical applications. *Annu Rev Med* 48:253–266
9. Borbély AA (1982) A two process model of sleep regulation. *Hum Neurobiol* 1:195–204
10. Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. *Sleep Med Rev* 10:49–62
11. Tononi G, Cirelli C (2003) Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 62:143–150
12. Cajochen C, Wyatt JK, Czeisler CA, Dijk DJ (2002) Separation of circadian and wake duration-dependent modulation of EEG activation during wakefulness. *Neuroscience* 114:1047–1060
13. Dijk DJ (1999) Reply to technical note: nonlinear interactions between circadian and homeostatic processes: models or metrics? *J Biol Rhythms* 14:604–605
14. Czeisler CA, Buxton OM, Khalsa SBS (2005) The human circadian timing system and sleep-wake regulation. In: Kryger MH, Roth T, Dement W (eds) *Principles and practice of sleep medicine*, 4th edn. Philadelphia, Elsevier, pp 375–394
15. Reppert SM, Weaver DR (2002) Coordination of circadian timing in mammals. *Nature* 418:935–941
16. Moore RY (1983) Organization and function of a central nervous system circadian oscillator: the suprachiasmatic hypothalamic nucleus. *Fed Proc* 42:2783–2789
17. Klein DC, Moore RY, Reppert SM (1991) *Suprachiasmatic nucleus: the mind's clock*. Oxford University Press, New York

18. Berson DM, Dunn FA, Takao M (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295:1070–1073
19. Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MD (2000) A novel human opsin in the inner retina. *J Neurosci* 20:600–605
20. Wirz-Justice A (2007) How to measure circadian rhythms in human. *Mediographia* 29:84–90
21. Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J (2000) Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol* 164:R1–R6
22. Berson DM (2003) Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci* 26:314–320
23. Provencio I, Rollag MD, Castrucci AM (2002) Photoreceptive net in the mammalian retina. *Nature* 415:493–494
24. Moore RY, Lenn NJ (1972) A retinohypothalamic projection in the rat. *J Comp Neurol* 146:1–9
25. Meyer-Bernstein EL, Morin LP (1996) Differential serotonergic innervation of the suprachiasmatic nucleus and the intergeniculate leaflet and its role in circadian rhythm modulation. *J Neurosci* 16:2097–2111
26. Cohen RA, Albers HE (1991) Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: a case study. *Neurology* 41:726–729
27. Inouye ST, Kawamura H (1979) Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. *Proc Natl Acad Sci U S A* 76:5962–5966
28. Moore R (2007) Suprachiasmatic nucleus in sleep-wake regulation. *Sleep Med* 8:27–33
29. Saper CB, Chou TC, Scammell TE (2001) The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci* 24:726–731
30. Mc Carley RW (2007) Neurobiology of REM and NREM sleep. *Sleep Med* 8:302–330
31. Llinas R, Steriade M (2006) Bursting of thalamic neurons and states of vigilance. *J Neurophysiol* 95:3297–3308
32. Abrahamson EE, Leak RK, Moore RY (2001) The suprachiasmatic nucleus projects to posterior hypothalamic arousal systems. *Neuroreport* 12:435–440
33. Deboer T, Overeem S, Visser NAH, Duindam H, Frölich M, Lammers GJ, Meijer JH (2004) Convergence of circadian and sleep regulatory mechanisms on hypocretin-1. *Neuroscience* 129:727–732
34. Yoshida Y, Fujiki N, Nakajima T, Ripley B, Matsumura H, Yoneda H, Mignot E, Nishino S (2001) Fluctuation of extracellular hypocretin-1 (orexin A) levels in the rat in relation to the light-dark cycle and sleep-wake activities. *Eur J Neurosci* 14:1075–1081
35. Zeitzer JM, Buckmaster CL, Parker KJ, Hauck CM, Lyons DM, Mignot E (2003) Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. *J Neurosci* 23:3555–3560
36. Brisbare-Roch C, Dingemans J, Koberstein R, Hoever P, Aissaoui H, Flores S (2007) Promotion of sleep by targeting the orexin system in rats, dogs and humans. *Nature* 12:150–155
37. Mistlberger RE (2005) Circadian regulation of sleep in mammals: role of the suprachiasmatic nucleus. *Brain Res Rev* 49:429–454
38. Moore RY (1996) Neural control of the pineal gland. *Behav Brain Res* 73:125–130
39. Czeisler CA, Gooley J (2007) Sleep and circadian rhythms in humans. *Cold Spring Harb Symp Quant Biol* 72:579–597
40. Cajochen C, Münch M, Knoblach V, Blatter K, Wirz-Justice A (2006) Age-related changes in the circadian and homeostatic regulation of human sleep. *Chronobiol Int* 23:1–14
41. Dibner C, Sage D, Unser M, Bauer C, d'Esmond T, Naef F, Schibler U (2008) Circadian gene expression is resilient to large fluctuations in overall transcription rates. *EMBO J* 27:1282–1293
42. Schibler U, Ripperger J, Brown SA (2003) Peripheral circadian oscillators in mammals: time and food. *J Biol Rhythms* 18:250–260
43. Mc Carley RW, Massaquoi SG (1992) Neurobiological structure of the revised limit cycle reciprocal interaction model of REM cycle control. *J Sleep Res* 1:132–137
9. The Circadian Clock and the Homeostatic Hourglass
44. Saper CB, Cano G, Scammell TE (2005) Homeostatic, circadian, and emotional regulation of sleep. *J Comp Neurol* 493:92–98
45. Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. *Nature* 437:1257–1263
46. Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J (2003) Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *J Neurosci* 23:10691–10702
47. Dijk DJ, Duffy JF, Czeisler CA (1992) Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J Sleep Res* 1:112–117
48. Dijk DJ (1995) EEG slow waves and sleep spindles: windows on the sleeping brain. *Behav Brain Res* 69:109–116
49. Jewett ME, Rimmer DW, Duffy JF, Klerman EB, Kronauer RE, Czeisler CA (1997) Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. *Am J Physiol Regul Integr Comp Physiol* 273:R1800–R1809
50. Van Dongen HPA, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26:117–126
51. Lockley SW, Cronin JW, Evans EE, Cade BE, Lee CJ, Landrigan CP, Rothschild JM, Katz JT, Lilly CM, Stone PH, Aeschbach D, Czeisler CA, the Harvard Work Hours, H.A.S.G. (2004) Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med* 351:1829–1837
52. Brunner DP, Dijk DJ, Borbély AA (1993) Repeated partial sleep deprivation progressively changes the EEG during sleep and wakefulness. *Sleep* 16:100–113
53. Dijk DJ, Hayes B, Czeisler CA (1993) Dynamics of electroencephalographic sleep spindles and slow wave activity in men: effect of sleep deprivation. *Brain Res* 626:190–199
54. Cajochen C, Foy R, Dijk DJ (1999) Frontal predominance of a relative increase in sleep delta and theta EEG activity after sleep loss in humans. *Sleep Res Online* 2:65–69
55. Borbély AA, Baumann F, Brandeis D, Strauch I, Lehmann D (1981) Sleep deprivation: effect on sleep stages and EEG power density in man. *Electroencephalogr Clin Neurophysiol* 51:483–495
56. Cajochen C, Knoblach V, Kräuchi K, Renz C, Wirz-Justice A (2001) Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure. *Neuroreport* 12:2277–2281
57. Werth E, Dijk DJ, Acherermann P, Borbély AA (1996) Dynamics of the sleep EEG after an early evening nap: experimental data and simulations. *Am J Physiol Regul Integr Comp Physiol* 271:501–510
58. Werth E, Acherermann P, Borbély AA (1996) Brain topography of the human sleep EEG: Antero-posterior shifts of spectral power. *Neuroreport* 8:123–127
59. Finelli LA, Baumann H, Borbély AA, Acherermann P (2000) Dual electroencephalogram markers of human sleep homeostasis: correlation between theta activity in waking and slow-wave activity in sleep. *Neuroscience* 101:523–529
60. Knoblach V, Kräuchi K, Renz C, Wirz-Justice A, Cajochen C (2002) Homeostatic control of slow-wave and spindle frequency activity during human sleep: effect of differential sleep pressure and brain topography. *Cereb Cortex* 12:1092–1100
61. Borbély AA, Acherermann P (2000) Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. W B Saunders Company, Philadelphia, pp 377–390
62. Rétey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP (2005) A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. *Proc Natl Acad Sci U S A* 102:15676–15681
63. Rétey JV, Adam M, Gottselig JM, Khatami R, Dürr R, Acherermann P, Landolt HP (2006) Adenosinergic mechanisms contribute to individual differences in sleep deprivation-induced changes in neurobehavioral function and brain rhythmic activity. *J Neurosci* 26:10472–10479
64. Landolt HP (2008) Sleep homeostasis: A role for adenosine in humans? *Biochem Pharmacol* 75:2070–2079

65. Huston JP, Haas HL, Boix F, Pfister MUD, Schrader J (1996) Extracellular adenosine levels in neostriatum and hippocampus during rest and activity periods of rats. *Neuroscience* 73:99–107
66. Murillo-Rodriguez E, Blanco-Centurion C, Gerashchenko D, Salin-Pascual RJ, Shiromani P (2004) The diurnal rhythm of forebrain of young and adenosine levels in the basal old rats. *Neuroscience* 123:361–370
67. Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ (2000) Adenosine modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state. *Behav Brain Res* 115:183–204
68. Basheer R, Strecker RE, Thakkar MM, McCarty RW (2004) Adenosine and sleep–wake regulation. *Prog Neurobiol* 73:379–396
69. Chamberlin NL, Arrigoni E, Chou TC, Scammell TE, Greene RW, Saper CB (2003) Effects of adenosine on GABAergic synaptic inputs to identified ventrolateral preoptic neurons. *Neuroscience* 119:913–918
70. Morairty S, Rainnie D, McCarty R, Greene RW (2004) Disinhibition of ventrolateral preoptic area sleep-active neurons by adenosine: a new mechanism for sleep promotion. *Neuroscience* 123:451–457
71. Timofeev I, Grenier F, Steriade M (2001) Disfacilitation and active inhibition in the neocortex during the natural sleep–wake cycle: an intracellular study. *Proc Natl Acad Sci U S A* 98:1924–1929
72. Maret S, Dorsaz S, Gurcel L, Praderwand S, Petit B, Pfister C, Hagenbuchle O, O'Hara BF, Franken P, Tafti M (2007) Homer1a is a core brain molecular correlate of sleep loss. *Proc Natl Acad Sci U S A* 104:20090–20095
73. Compte A, Sanchez-Vives MV, McCormick DA, Wang XJ (2003) Cellular and network mechanisms of slow oscillatory activity (<1 Hz) and wave propagations in a cortical network model. *J Neurophysiol* 89:2707–2725
74. Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ (2002) Model of thalamocortical slow-wave sleep oscillations and transitions to activated states. *J Neurosci* 22:8691–8704
75. Hill S, Tononi G (2005) Modeling sleep and wakefulness in the thalamocortical system. *J Neurophysiol* 93:1671–1698
76. Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G (2004) The sleep slow oscillation as a travelling wave. *J Neurosci* 24:6862–6870
77. Cajochen C, Brunner DP, Kräuchi K, Graw P, Wirz-Justice A (1995) Power density in theta/alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep* 18:890–894
78. Cajochen C, Kräuchi K, Knoblauch V, Renz C, Rössler A, Balesrieri G, Dattler MF, Graw P, Wirz-Justice A (2001) Dynamics of frontal low EEG-activity, subjective sleepiness and body temperature under high and low sleep pressure. *Neuroreport* 20:2277–2281
79. Aeschbach D, Matthews JR, Postolache TT, Jackson MA, Giesen HA, Wehr TA (1997) Dynamics of the human EEG during prolonged wakefulness: evidence for frequency-specific circadian and homeostatic influences. *Neurosci Lett* 239:121–124
80. Dijk DJ, Beersma DGM, Daan S (1987) EEG power density during nap sleep: reflection of an hourglass measuring the duration of prior wakefulness. *J Biol Rhythms* 2:207–219
81. Cirelli C, Tononi G (2000) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J Neurosci* 20:9187–9194
82. Cirelli C, Pompeiano M, Tononi G (1996) Neuronal gene expression in the waking state: a role for the locus coeruleus. *Science* 274:1211–1215
83. Kopp C, Longordo F, Nicholson JR, Lüthi A (2006) Insufficient sleep reversibly alters bidirectional synaptic plasticity and NMDA receptor function. *J Neurosci* 26:12456–12465
84. Krueger JM, Obál F (1993) A neuronal group theory of sleep function. *J Sleep Res* 2:63–69
85. Krueger JM, Obál F Jr, Kapás L, Fang J (1995) Brain organization and sleep function. *Behav Brain Res* 69:177–185
86. Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G (2008) Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nat Neurosci* 11:200–208
- 9 The Circadian Clock and the Homeostatic Hourglass
87. Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G (2007) Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. *Sleep* 30:1631–1642
88. Gruetzendler J, Kasthuri N, Gan WB (2002) Long-term dendritic spine stability in the adult cortex. *Nature* 420:812–816
89. Dijk DJ, Edgar DM (1999) Circadian and homeostatic control of wakefulness and sleep. In: Turek FW, Zee PC (eds) *Regulation of sleep and circadian rhythms*, vol 133. Marcel Dekker, Inc, New York Basel, pp 111–147
90. Dijk DJ, Czeisler CA (1995) Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and spindle activity in humans. *J Neurosci* 15:3526–3538
91. Kronauer RE, Czeisler CA, Pilato SF, Moore-Ede MC, Weitzman ED (1982) Mathematical model of the human circadian system with two interacting oscillators. *Am J Physiol Regul Integr Comp Physiol* 242:R3–R17
92. Daan S, Beersma DGM, Borbély AA (1984) Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol Regul Integr Comp Physiol* 246:R161–R178
93. Edgar DM, Dement WC, Fuller CA (1993) Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep–wake regulation. *J Neurosci* 13:1065–1079
94. Cajochen C, Khalsa SBS, Wyatt JK, Czeisler CA, Dijk DJ (1999) EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *Am J Physiol Regul Integr Comp Physiol* 277:R640–R649
95. Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, Czeisler CA (1992) Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *J Sleep Res* 1:24–29
96. Dijk DJ, Czeisler CA (1994) Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett* 166:63–68
97. Liu C, Weaver D, Jin X, Shearman L, SM R (1997) Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* 19:91
98. Barinaga M (1997) How jet-lag hormone does double duty in the brain. *Science* 277:480
99. Czeisler CA, Zimmerman JC, Ronda JM, Moore-Ede MC, Weitzman ED (1980) Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep* 2:329–346
100. Tobler I, Borbély AA, Groos G (1983) The effect of sleep deprivation on sleep in rats with suprachiasmatic lesions. *Neurosci Lett* 21:49–54
101. Achermann P (1999) Technical note: a problem with identifying nonlinear interactions of circadian and homeostatic processes. *J Biol Rhythms* 14:602–603
102. Deboer T, Vansteensel MJ, Déjari L, Meijer JH (2003) Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci* 6:1086–1090
103. Zulley J, Wever R, Aschoff J (1981) The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. *Pflügers Arch* 391:314–318
104. Aschoff J, Von Goetz C, Wildgruber C, Wever RA (1986) Meal timing in humans during isolation without time cues. *J Biol Rhythms* 1:151–162
105. Aschoff J, Gerecht U, Wever R (1967) Desynchronization of human circadian rhythms. *Jpn J Physiol* 17:450–457
106. Zulley J (1980) Distribution of REM sleep in entrained 24 hour and free-running sleep–wake cycles. *Sleep* 2:377–389
107. Zimmerman JC, Czeisler CA, Laxminarayan S, Knauer RS, Weitzman ED (1980) REM density is dissociated from REM sleep timing during free-running sleep episodes. *Sleep* 2:409–415
108. Weitzman ED, Czeisler CA, Zimmerman JC, Ronda JM (1980) Timing of REM and stages 3+4 sleep during temporal isolation in man. *Sleep* 2:391–407
109. Hiddinga AE, Beersma DGM, Van Den Hoofdakker RH (1997) Endogenous and exogenous components in the circadian variation of core body temperature in humans. *J Sleep Res* 6:156–163

110. Wyatt JK, Ritz-De Cecco A, Czeisler CA, Dijk DJ (1999) Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am J Physiol Regul Integr Comp Physiol* 277:R1152-R1163
111. Hull JT, Wright KP Jr, Czeisler CA (2003) The influence of subjective alertness and motivation on human performance independent of circadian and homeostatic regulation. *J Biol Rhythms* 18:329-338
112. Dijk DJ, Shanahan TL, Duffy JF, Ronda JM, Czeisler CA (1997) Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *J Physiol* 505:851-858
113. Wyatt J, Dijk D, Ritz-De Cecco A, Ronda J, Czeisler C (2006) Sleep facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent. *Sleep* 29:609-610
114. Cajochen C, Brunner DP, Kräuchi K, Graw P, Wirz-Justice A (2000) EEG and subjective sleepiness during extended wakefulness in seasonal affective disorder: circadian and homeostatic influences. *Biol Psychol* 47:610-617
115. Steriade M, McCormick DA, Sejnowski TJ (1993) Thalamic oscillations in the sleeping and aroused brain. *Science* 262:679-685
116. Amzica F, Steriade M (1998) Electrophysiological correlates of sleep delta waves. *Electroencephalogr Clin Neurophysiol* 107:69-83
117. Siapas AG, Wilson MA (1998) Coordinated interactions between hippocampal ripples and cortical spindles during slow-wave sleep. *Neuron* 21:1123-1128
118. Schibler U (2005) The daily rhythms of genes, cells and organs. *Biological clocks and circadian timing in cells*. *EMBO J* 6:9-13
119. Schibler U, Naef F (2005) Cellular oscillators: rhythmic gene expression and metabolism. *Curr Opin Cell Biol* 17:223-229
120. Ebisawa T, Uchiyama M, Kajimura N, Mishima K, Kamei Y, Katoh M, Watanabe T, Sekimoto M, Shibui K, Kim K, Kudo Y, Ozeki Y, Sugishita M, Toyoshima R, Inoue Y, Yamada N, Nagase T, Ozaki N, Ohara O, Ishida N, Okawa M, Takahashi K, Yamachi T (2001) Association of structural polymorphisms in the human period 3 gene with delayed sleep phase syndrome. *EMBO report* 2:342-346
121. Naylor E, Bergmann BM, Krauski K, Zee PC, Takahashi JS, Viaterna MH, Turek FW (2000) The circadian clock mutant after sleep homeostasis in the mouse. *J Neurosci* 20:8138-8143
122. Antoch M, Song E, Chang A, Viaterna M, Zhao Y, Wilsbacher L, Sangoram A, King D, Pinto L, Takahashi J (1997) Functional identification of the mouse circadian clock gene by transgenic BAC rescue. *Cell* 89:655-667
123. Kopp C, Albrecht U, Zheng B, Tobler I (2002) Homeostatic sleep regulation is preserved in mPer1 and mPer2 mutant mice. *Eur J Neurosci* 16:1099-1106
124. Franken P, Thomsen R, Heller HC, O'Hara BF (2007) A non-circadian role for clock-genes in sleep homeostasis: a strain comparison. *BMC Neurosci* 8:87-97
125. Boivin DB, James FO, Wu A, Cho-Park F, Xiong H, Sun ZS (2003) Circadian clock genes oscillate in human peripheral blood mononuclear cells. *Blood* 102:4143-4145
126. Archer SN, Viola AU, Kyriakopoulou V, von Schantz M, Dijk D (2008) Inter-Individual differences in habitual sleep timing and entrained phase of endogenous circadian rhythms of BMAL1, PER2 and PER3 mRNA in human leucocytes. *Sleep* 5:608-617
127. Viola AU, Archer SN, James LM, Groeger JA, Lo JCY, Skene DJ, Von Schantz M, Dijk DJ (2007) PER3 polymorphism predicts sleep structure and waking performance. *Curr Biol* 17:613-618
128. Dijk DJ, Franken P (2005) Interaction of sleep homeostasis and circadian rhythmicity: Dependent or independent systems? In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine, 4th edn. Elsevier, Philadelphia, pp 418-434
129. Mecacci L, Zani A (1983) Morningness-eveningness preferences and sleep-waking diary data of morning and evening types in student and worker samples. *Ergonomics* 26:1147-1153
130. Duffy JF, Dijk DJ, Hall E, Czeisler CA (1999) Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. *J Invest Med* 47:141-150
9. The Circadian Clock and the Homeostatic Hourglass
131. Mongrain V, Lavoie S, Selmaoui B, Paquet J, Dumont M (2004) Phase relationships between sleep - wake cycle and underlying circadian rhythms in morningness - eveningness. *J Biol Rhythms* 19:248-257
132. Dijk DJ, Lockett SW (2002) Integration of human sleep-wake regulation and circadian rhythmicity. *J Appl Physiol* 92:852-862
133. Mongrain V, Carrier J, Dumont M (2004) Circadian and homeostatic sleep regulation in morningness-eveningness. *J Sleep Res* 15:162-166
134. Mongrain V, Carrier J, Dumont M (2006) Difference in sleep regulation between morning and evening circadian types as indexed by antero-posterior analyses of the sleep EEG. *Eur J Neurosci* 23:497-504
135. Schmidt C, Collette F, Leclercq Y, Sterpenich V, Vandewalle G, Berthomier P, Berthomier C, Phillips C, Tinguely G, Darsaud A, Gais S, Schabus M, Dessesilles M, Dang-Vu T.T, Salmon E, Baletau E, Dequeldre C, Luxen A, Maquet P, Cajochen C, Peigneux P (2009) Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area. *Science*, 324(5926):516-519
136. Aeschbach D, Cajochen C, Landolt H, Borbély AA (1996) Homeostatic sleep regulation in habitual short sleepers and long sleepers. *Am J Physiol Regul Integr Comp Physiol* 270:R41-R53
137. Aeschbach D, Sher L, TT P (2003) A longer biological night in long sleepers than in short sleepers. *Am J Physiol Endocrinol Metab* 88:26-30
138. Buysse DJ, Browman KE, Monk TH, Reynolds CF III, Fasiczka AL, Kupfer DJ (1992) Napping and 24-hour sleep/wake patterns in healthy elderly and young adults. *J Am Geriatr Soc* 40:779-786
139. Bliwise DL (1993) Sleep in normal aging and dementia. *Sleep* 16:40-81
140. Czeisler CA, Dumont M, Duffy JF, Steinberg JD, Richardson GS, Brown EN, Sánchez R, Rios CD, Ronda JM (1992) Association of sleep-wake habits in older people with changes in output of circadian pacemaker. *Lancet* 340:933-936
141. Duffy JF, Dijk DJ, Klerman BE, Czeisler CA (1998) Later endogenous circadian temperature nadir relative to an earlier wake time in older people. *Am J Physiol Regul Integr Comp Physiol* 275:R1478-R1487
142. Duffy JF, Czeisler CA (2002) Age-related change in the relationship between circadian period, circadian phase, and diurnal preference in humans. *Neurosci Lett* 318:117-120
143. Münch M, Knoblauch V, Blatter K, Schröder C, Schmitzler C, Kräuchi K, Wirz-Justice A, Cajochen C (2004) The frontal predominance in human EEG delta activity after sleep loss decreases with age. *Eur J Neurosci* 20:1402-1410
144. Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA (1999) Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *J Physiol* 516:611-627
145. Münch M, Knoblauch V, Blatter K, Schroder C, Schmitzler C, Kräuchi K, Wirz-Justice A, Cajochen C (2005) Age-related attenuation of the evening circadian arousal signal in humans. *Neurobiol Aging* 26:1307-1319
146. Münch M, Knoblauch V, Blatter K, Wirz-Justice A, Cajochen C (2007) Is homeostatic sleep regulation under low sleep pressure modified by age? *Sleep* 30:781-792
147. Wirz-Justice A (2003) Chronobiology and mood disorders. *Dialogues Clin Neurosci* 5:223-233
148. Van Someren EJW (2000) Circadian and sleep disturbances in the elderly. *Exp Gerontol* 35:1229-1237
149. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJG, Van Someren E (2008) Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities. *JAMA* 299:2642-2655
150. Van Someren EJW, Hagebeuk EEO, Lijzenga C, Scheltens P, De Rooij SEJA, Jonker C, Pot AM, Mirmiran M, Swaab DF (1996) Circadian rest-activity rhythm disturbances in Alzheimer's disease. *Biol Psychiatry* 40:259-270
151. Wu YH, Swaab DF (2006) Disturbance and strategies for reactivation of the circadian rhythm system in aging and Alzheimer's disease. *Sleep Med* 8:623-636

152. Ferrari E, Arcaini A, Gornati R, Pelanconi L, Cravello L, Fioravanti M, Solerte SB, Magri F (2000) Pineal and pituitary-adrenocortical function in physiological aging and in senile dementia. *Exp Gerontol* 35:1239–1250
153. Perlis ML, Giles DE, Buysse DJ, Thase ME, Tu X, Kupfer DJ (1997) Which depressive symptoms are related to which sleep electroencephalographic variables? *Biol Psychiatry* 42:904–913
154. Riemann D, Berger M, Voderholzer U (2001) Sleep and depression – results from psychobiological studies: an overview. *Biol Psychol* 57:67–103
155. Boivin DB (2000) Influence of sleep–wake and circadian rhythm disturbances in psychiatric disorders. *J Psychiatry Neurosci* 25:446–458
156. Lewy AJ, Lefler BJ, Emens JS, Bauer VK (2006) The circadian basis of winter depression. *Proc Natl Acad Sci U S A* 103:7414–7419
157. Chellappa SL, Araujo JF (2007) Sleep disorders and suicidal ideation in patients with depressive disorder. *Psychiatr Res* 153:131–136
158. Chellappa SL, Araujo JF (2006) Excessive daytime sleepiness in patients with depressive disorder. *Rev Bras Psiquiatr* 28:126–130
159. Fava M (2004) Daytime sleepiness and insomnia as correlates of depression. *J Clin Psychiatry* 65:27–32
160. Drennan MD, Klauber MR, Kripke DF, Goyette LM (1991) The effects of depression and age on the Horne–Ostberg morningness–eveningness score. *J Affect Disord* 23:93–98
161. Johansson C, Willett M, Smedh C, Ekholm J, Paunio T, Kiesepää T, Lichtermann D, Praszak-Rieder N, Neumeister A, Nilsson LG, Kasper S, Peltonen L, Adolfsson R, Schalling M, Partonen T (2003) Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* 28:734–739
162. Katzenberg D, Young T, Finn L, Lin L, King DP, Takahashi J (1998) A CLOCK polymorphism associated with human diurnal preference. *Sleep* 21:569–576
163. McClung CA (2007) Circadian genes, rhythms and the biology of mood disorders. *Pharmacol Thera* 114:222–232
164. Landolt HP, Raimo EB, Schnierow BJ, Kelsoc JR, Rapaport MH, Gillin JC (2001) Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. *Arch Gen Psychiatry* 58:268–276
165. Cajochen C (2007) Alerting effects of light. *Sleep Med Rev* 11:453–464
166. Cajochen C, Wyatt JK, Bonikowska M, Czeisler C, Dijk DJ (2000) Non-linear interaction between circadian and homeostatic modulation of slow eye movements during wakefulness in humans. *J Sleep Res* 9(S1):29

Chapter 10

Clocks, Brain Function, and Dysfunction

Céline Feillet and Urs Albrecht

10.1 Introduction

All living organisms on our planet experience daily and seasonal changes. The physiology of plants and animals is dynamically controlled to respond to these recurring fluctuations. Daily and seasonal modifications of the environmental conditions are predictable as long as the organism possesses a system allowing time tracking. Clocks provide an estimation of time and thus permit to anticipate environmental changes by preparing the organism through the initiation of cellular and physiological mechanisms before they are actually required. At the time those processes are needed, they are already running at full capacity.

Clocks represent a highly advantageous evolutionary feature and have been widely implicated in normal brain and physiological functions. They are connected to both afferent and efferent pathways, which allow them to “listen” to their environment and to “speak” to the rest of the organism. When the clock is impaired, it impacts on both the brain and peripheral organ physiology. In return, a dysfunction in physiology can dysregulate the clock, thus giving rise to secondary symptoms.

Clocks control the so-called “biological rhythms”, which can be characterized by their period (time separating two identical events) and separated into three groups: infradian rhythms, occurring less than once a day (seasonal rhythms are an example), circadian rhythms (from the latin *circa*: about and *dies*: a day) showing periods of about 24 h and ultradian rhythms with periods shorter than 24 h (e.g., sleep stages, heart beats). Here, we will essentially focus on circadian rhythms in the brain of rodents and humans.

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