Sleep Physiology, Circadian Rhythms, Waking Performance and the Development of Sleep-Wake Therapeutics

Derk-Jan Dijk and Hans-Peter Landolt

Contents

D.-J. Dijk (✉)
Surrey Sleep Research Centre, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK
e-mail: d.j.dijk@surrey.ac.uk

H.-P. Landolt
Institute of Pharmacology and Toxicology, Sleep and Health Zurich, University Center of Competence, University of Zurich, Zurich, Switzerland

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Abstract

Disturbances of the sleep-wake cycle are highly prevalent and diverse. The aetiology of some sleep disorders, such as circadian rhythm sleep-wake disorders, is understood at the conceptual level of the circadian and homeostatic regulation of sleep and in part at a mechanistic level. Other disorders such as insomnia are more difficult to relate to sleep regulatory mechanisms or sleep physiology. To further our understanding of sleep-wake disorders and the potential of novel therapeutics, we discuss recent findings on the neurobiology of sleep regulation and circadian rhythmicity and its relation with the subjective experience of sleep and the quality of wakefulness. Sleep continuity and to some extent REM sleep emerge as determinants of subjective sleep quality and waking performance. The effects of insufficient sleep primarily concern subjective and objective sleepiness as well as vigilant attention, whereas performance on higher cognitive functions appears to be better preserved albeit at the cost of increased effort. We discuss age-related, sex and other trait-like differences in sleep physiology and sleep need and compare the effects of existing pharmacological and non-pharmacological sleep- and wake-promoting treatments. Successful non-pharmacological approaches such as sleep restriction for insomnia and light and melatonin treatment for circadian rhythm sleep disorders target processes such as sleep homeostasis or circadian rhythmicity. Most pharmacological treatments of sleep disorders target specific signalling pathways with no well-established role in either sleep homeostasis or circadian rhythmicity. Pharmacological sleep therapeutics induce changes in sleep structure and the sleep EEG which are specific to the mechanism of action of the drug. Sleep- and wake-promoting therapeutics often induce residual effects on waking performance and sleep, respectively. The need for novel therapeutic approaches continues not at least because of the societal demand to sleep and be awake out of synchrony with the natural light-dark cycle, the high prevalence of sleep-wake disturbances in mental health disorders and in neurodegeneration. Novel approaches, which will provide a more comprehensive description of sleep and allow for large-scale sleep and circadian physiology studies in the home environment, hold promise for continued improvement of therapeutics for disturbances of sleep, circadian rhythms and waking performance.

Keywords

Circadian · Drug discovery · REM sleep · Sleep continuity · Sleep quality · Slow-wave sleep · Wake quality

1 Quantifying the Quality of Sleep and Wakefulness

1.1 A Multivariate Phenomenology

Sleep is a major determinant of well-being, mental and physical health and understanding sleep-health relations, and sleep disorders are dependent on adequate quantification of sleep. Sleep and wake states are characterised by constellations of variables representing nearly all levels of system organisation ranging from gene expression (O'Callaghan et al. 2018), neuronal firing patterns (McKillop and Vyazovskiy 2018), neurotransmitter release (Zant et al. 2016; Luppi and Fort 2018), endocrine and autonomic nervous system status (Morris et al. 2012; Fink et al. 2018), body and brain temperature (Landolt et al. 1995), responsiveness to external stimuli (Ermis et al. 2010), motor behaviour (Horner and Peever 2017) to changes in consciousness (Casali et al. 2013). Which variables are essential to sleep quality and how these variables contribute to sleep's associations with well-being, physical health and brain function remain, however, largely unknown even though several hypotheses have been proposed.

Here we will summarise some recent developments in research on sleep physiology, circadian rhythms and waking performance and their interrelations in humans without sleep complaints and discuss some implications for the understanding and development of non-pharmacological and pharmacological therapeutics for sleep and circadian disorders.

1.1.1 Sleep

Sleep has a rich phenomenology consisting of both subjective and objective aspects, and new facets continue to be reported. In humans, sleep comprises the subjective experience of the cessation of consciousness (falling asleep), the presence of dreams and nightmares or the feeling of not having slept all night. After waking up, the sleep experience can be reported as sleep quality and sleep depth. At another level sleep is a state of the brain and the body which in humans and animals can be quantified by objective behavioural criteria such as immobility and arousal thresholds and by a wide range of physiological variables. The electroencephalogram, electromyogram, electrooculogram, electrocardiogram, endocrine parameters, and respiratory parameters are among the physiological variables most commonly recorded in laboratory studies of human sleep. A recording of these state variables is referred to as a polysomnogram (PSG) (Berry et al. 2017) (see Fig. 1). Currently sleep is primarily quantified by sleep staging based on EEG, EMG, and EOG signals. Sleep is subdivided into non-rapid eye movement (NREM) sleep and rapid eye movement sleep (REM). In the current sleep staging guidelines for humans, NREM sleep will be further segmented in N1–N3 with N3 often referred to as slow-wave sleep (SWS). Previously NREM sleep was subdivided in stages 1–4 with stages 3 + 4 being combined as SWS. After sleep staging the sleep process is quantified by variables such as the latency to sleep onset, the duration of the various sleep stages, the relative contribution of sleep stages to total sleep time or the transitions between sleep stages. NREM sleep typically precedes REM sleep, and the ultradian cycle of the alternation

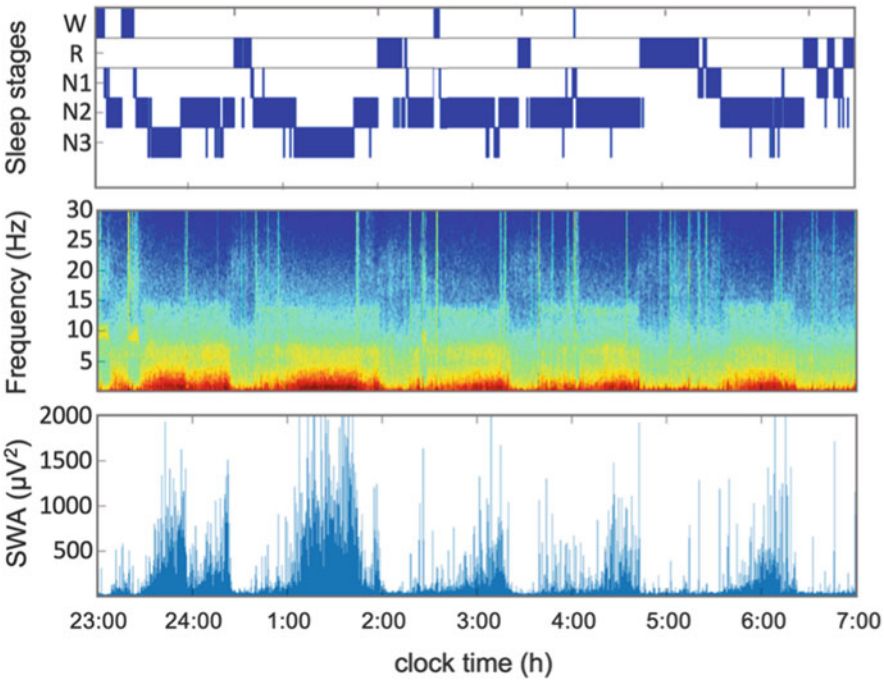

Fig. 1 Nocturnal sleep in a young adult. Hypnogram, spectrogram and time course of slow-wave activity (SWA = EEG power in the 0.75–4.5 Hz range). *W* wakefulness, *R* REM sleep, *N1–N3* NREM sleep stages 1–3

of NREM and REM sleep is one characteristic of interest. The duration of the NREM-REM cycle scales in a lawful manner to body and brain size sleep suggesting that it is closely linked to a primordial but as yet unknown function of sleep (Frank and Heller 2019). Sleep can be further characterised by its continuity, i.e. are sleep and wake episodes consolidated or are they interrupted by brief intrusions of the other state. Sleep continuity can be quantified as sleep efficiency (i.e. total sleep time/time in bed), wake after sleep onset, the number of awakenings, EEG arousals or the distribution of the duration of uninterrupted sleep bouts as assessed by survival analysis or other methods (Klerman et al. 2013; Svetnik et al. 2018).

Signal analysis-based approaches such as spectral analysis have been used to further characterise sleep although these approaches are still not standard in most research and clinical studies. Quantification of specific electrophysiological phenomena such as slow waves and sleep spindle oscillations (Dijk et al. 1993; Lazar et al. 2015), muscle tone (Brunner et al. 1990a; Jeppesen et al. 2018) or heart rate variability (Yang et al. 2018; Viola et al. 2008a) and changes thereof across the sleep episode or in response to pharmacological and non-pharmacological sleep manipulations have provided new insights into the sleep process. Quantification of slow waves through spectral analysis as power density in the low-frequency range

(0.75–4.5 Hz) and commonly referred to as slow-wave activity (SWA) has formed the basis for quantification of the homeostatic process in the two-process model of sleep regulation (Borbély 1982; Daan et al. 1984). Topographical analyses using multi-electrode EEG recordings have identified local aspects of sleep which may be relevant to local recovery processes (Kattler et al. 1994; Huber et al. 2006), memory consolidation (Rasch and Born 2013), the dream process (Siclari et al. 2017) or maybe the lack of cessation of consciousness despite the presence of global sleep as observed in insomnia (Riedner et al. 2016). Analyses of synchronisation across multiple EEG derivations and EEG frequencies have shown that the three vigilance states (Wakefulness, NREM and REM) are very different with REM sleep being the most synchronised state (Achermann et al. 2016), even though the REM sleep EEG is commonly described as desynchronised. Analyses of the temporal characteristics of the EEG have revealed phenomena such as phase locking between slow oscillations and sleep spindles (Klinzing et al. 2016) and ultra-slow oscillatory processes in spindle activity with periods of approximately 50–75 s (Lecci et al. 2017; Lazar et al. 2018).

1.1.2 Wakefulness

Sleep research tacitly assumes that the quality of wakefulness relates, at least in part, to the quality of sleep, although the reverse pathway is also plausible. Wakefulness is subjectively experienced, with alertness, sleepiness and fatigue being commonly used words to describe the quality of wakefulness. The subjective quality of wakefulness in terms of perceived alertness can be quantified with the Karolinska sleepiness scale (Akerstedt et al. 2017) or the Epworth sleepiness scale (Johns 1991) or objectively assessed as the ability to stay awake using the maintenance of wakefulness test or the propensity to fall asleep by the multiple sleep latency test (Sullivan and Kushida 2008). The quality of wakefulness can be characterised by absence or intrusion of sleep like electroencephalographic features such as theta activity (Greneche et al. 2008; Cajochen et al. 1995). The quality of wakefulness can be measured as the ability to remain vigilant and respond to stimuli in simple, and rather boring, test conditions such as in the psychomotor vigilance test (Lim and Dinges 2008). Finally, the quality of wakefulness may be assessed by the performance on tasks probing more complicated brain functions like working memory, executive function tests and the effort it takes to perform these tasks (Lo et al. 2012; Groeger et al. 2014) and tasks related to our professional and social life, e.g. driving (Shekari Soleimanloo et al. 2017).

The quality of wakefulness immediately following sleep is of special interest. Following the transition from sleep to wakefulness as defined by the PSG, it takes the brain some time to reach full waking performance (Balkin et al. 2002; Santhi et al. 2013). This process, referred to as sleep inertia, is relevant in operational conditions, for example, when pilots take naps on long haul flights, and may be exacerbated by non-pharmacological (e.g. sleep restriction) (Balkin and Badia 1988) and pharmacological (Boyle et al. 2012a; Cohen et al. 2010a) treatments of sleep disturbances.

Understanding how the different dimensions of sleep and wakefulness are interrelated, e.g. which physiologic aspect of sleep predicts the subjective quality of sleep, how sleep physiology relates to the quality of waking and how sleep- and wake-promoting therapeutics affect wake and sleep quality, respectively, is one of the challenges of sleep research and sleep medicine.

We will first discuss how sleep physiology is regulated in response to sleep loss.

2 Homeostatic Regulation of Sleep Physiology

Homeostatic regulation of sleep physiology has been investigated since the early days of modern sleep research. Most frequently used protocols are total sleep deprivation, e.g. not sleeping at all for 40 or 64 h, repeated partial sleep deprivation (e.g. a week of only 6 h of sleep per day), sleep extension, selective sleep deprivation (e.g. suppression of SWS) and nap studies. Sleep propensity and sleep structure of recovery sleep was the primary outcome measure in many of these studies. A major limitation of most of these studies is that time in bed during recovery sleep was restricted and sleep termination was thus not spontaneous. As a consequence the homeostatic regulation of human sleep duration is not well documented.

2.1 Sleep Propensity and Sleep Continuity

Total sleep deprivation, repeated partial sleep deprivation and selective disruption of SWS all lead to an increase in subjective and objective sleep propensity, i.e. subjective sleepiness and a reduction in the latency to sleep onset. These interventions also lead to a reduction in wake after sleep onset and the number of awakenings, i.e. sleep continuity increases with increasing homeostatic sleep pressure. Increasing time in bed, i.e. extending the nocturnal sleep opportunity (Bei et al. 2014, 2017; Skorucak et al. 2018) or taking naps and in particular naps in the later part of the day (Werth et al. 1996), leads to increases in the objective and subjective latency to sleep onset and also leads to a reduction in sleep continuity. Remarkably, a large-scale observational study in the community indicated that short sleep is associated with lower sleep efficiency and more awakenings, i.e. a pattern opposite to that observed in interventional laboratory studies (Akerstedt et al. 2019). This probably implies that short sleep in the community is caused by 'sleep problems' rather than imposed sleep restriction.

2.2 NREM Sleep, SWS and SWA

In humans NREM sleep is subdivided into N1, N2 and slow-wave sleep. Slow-wave sleep and slow-wave activity, i.e. EEG power density in the low-frequency range content of naps increases as naps are taken later in the day (Dijk et al. 1987a), nocturnal slow-wave sleep is increased after acute total sleep deprivation

(Borbély et al. 1981), and slow-wave sleep in nocturnal sleep is decreased after a nap taken later in the day (Werth et al. 1996). Slow-wave sleep is only marginally increased after repeated partial sleep deprivation (Brunner et al. 1993). Slow-wave sleep deprivation leads to an increase of SWS in subsequent undisturbed sleep (Dijk et al. 1987b; Dijk and Beersma 1989). These responses are consistent with a saturating exponential increase of slow-wave sleep pressure with time awake (Dijk et al. 1990a) and an approximately exponential decline of slow-wave sleep pressure during sleep (Dijk et al. 1990b; Achermann et al. 1993). The time constants of these functions are such that most of the dynamic range of slow-wave sleep is covered within a normal 24-h sleep-wake cycle (Skorucak et al. 2018; Rusterholz et al. 2010). This implies that SWS is primarily responsive to acute variation in sleep and wakefulness. Some data suggest that increasing the intensity of wakefulness through physical exercise or exposure to particular waking experiences may lead to global or local enhancement of slow-wave sleep (Horne and Moore 1985; Melancon et al. 2015; Huber et al. 2004).

2.3 REM Sleep

The homeostatic regulation of REM sleep is different from NREM sleep. Acute total sleep deprivation has no major effect on REM sleep during subsequent recovery sleep when the duration of recovery sleep is experimentally constrained (Borbély et al. 1981). Repeated partial sleep deprivation, which is not associated with a loss of SWS but is associated with a loss of REM sleep, leads to a REM sleep rebound during recovery sleep (Brunner et al. 1990b; Skorucak et al. 2018). REM sleep deprivation in the beginning of the sleep period leads to a rebound in the second half of the same sleep period (Beersma et al. 1990). A typical characteristic of REM sleep deprivation is that attempts to initiate REM sleep occur in clusters and increases in the course of REM sleep deprivation (Endo et al. 1998). A pronounced REM sleep rebound was also observed during withdrawal from REM sleep suppressing antidepressants (Landolt and de Boer 2001). Some authors have suggested that REM sleep's homeostatic regulation is primarily related to NREM sleep preceding REM sleep rather than preceding wakefulness (see Frank and Heller 2019).

It is often tacitly assumed that sleep after sleep loss is good sleep which implies that more SWS, shorter sleep latencies and fewer awakenings are the hallmarks of good sleep. Whether more SWS or more REM sleep is a positive characteristic depends on whether one considers total sleep deprivation or partial sleep deprivation the more natural challenge of sleep regulatory systems.

2.4 Age- and Sex-Related Differences in Sleep Physiology

Slow-wave sleep and slow-wave activity decline during the adult life span but so do sleep spindle activity and REM sleep (Schwarz et al. 2017; Della Monica et al. 2018). Age-related reductions in REM sleep are probably underestimated because as

mentioned, in most studies, time in bed was limited. Under ad libitum sleep conditions, age-related reductions in REM sleep may be as large as reductions in SWS (Klerman and Dijk 2008). Apart from changes in SWS and REM sleep, reductions in sleep efficiency and increases in the number of awakenings are consistently observed in healthy ageing. At the same time, the subjective quality of sleep as reported by the sleeper, rather than construed by sleep researchers, may not change much in healthy ageing (Akerstedt et al. 2016; Della Monica et al. 2018), and this is commonly interpreted as a habituation to reduced objective sleep quality.

Sex differences in sleep physiology primarily concern slow-wave sleep with women spending more time in slow-wave sleep and higher slow-wave activity (Dijk et al. 1989a; Svetnik et al. 2017). The age-related decline in SWA appears shallower in women than in men. Sleep continuity measures are not markedly different between the sexes (Carrier et al. 2017; Della Monica et al. 2018).

2.5 Sleep Physiology and the Subjective Quality of Sleep

A personal experience-oriented approach to sleep may define good sleep as sleep associated with sleep satisfaction or satisfactory alertness during the subsequent waking day. Sleep research may aim to understand how subjective sleep quality relates to objective aspects of sleep. When we only consider recent observational studies in which sleep in participants without sleep complaints were assessed by polysomnography, the consensus conclusion across these cross-sectional studies is that sleep efficiency/continuity is a significant determinant of reported sleep quality and the feeling of being refreshed upon awakening (Akerstedt et al. 2016; Kaplan et al. 2017a, b; Della Monica et al. 2018). This association is present across the adult life span and according to one study is much stronger in women than in men (Della Monica et al. 2018). Remarkably, these studies imply that deep sleep, i.e. SWS or N3, is not a main determinant of subjective measures of sleep quality. In one study REM sleep duration was positively associated with subjective sleep quality (Della Monica et al. 2018) (see Fig. 2). It should be noted that even though significant PSG predictors were identified, they explained only a small portion of the variance in subjective sleep quality.

2.6 Sleep Physiology and the Quality of Wakefulness

2.6.1 Observational Studies

How sleep is related to the quality of subsequent wakefulness is a key question when we consider sleep as a process of recovery and preparation for the next wake episode. Total sleep time is a correlate of subsequent waking quality such that in healthy participants, self-reported and objectively assessed total sleep time associates with alertness the next day as assessed by the multiple sleep latency test (MSLT) (Klerman and Dijk 2005). Longitudinal studies have demonstrated that the night-to-night variation in sleep duration is associated with subjective sleepiness

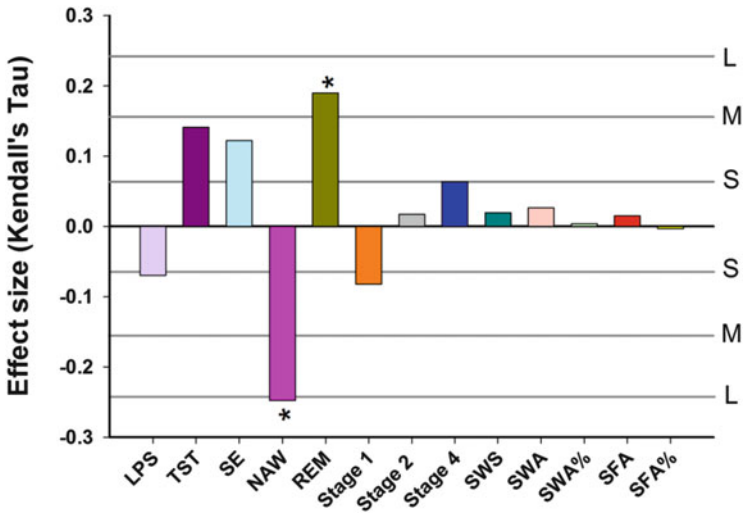

Fig. 2 Contribution of polysomnographically determined sleep variables to subjective sleep quality. Effect size is quantified with Kendall's tau after correcting for age and sex. Vertical lines represent large, medium and small effect sizes. *NAW* number of awakenings, *REM* rapid eye movement sleep, *TST* total sleep time, *SEFF* sleep efficiency, *LPS* latency to persistent sleep, *SWS* slow-wave sleep, *SWA* slow-wave activity, *SFA* sleep spindle frequency activity. Modified from Della Monica et al. (2018)

(Akerstedt et al. 2013). When we consider performance on specific tasks as an indicator of the quality of wakefulness, the picture emerging from observational studies in which sleep duration was assessed by self-report becomes more complex. For example, in a large-scale Internet-based study, it was found that both short and long sleep were associated with reduced performance on reasoning and verbal skills and no relationship between sleep duration and short-term memory performance was observed (Wild et al. 2018). Similarly, in an analysis of UK biobank data, both short and long sleep (self-reported) were associated with impaired performance, and the complaint of insomnia was not associated with reduced performance (Kyle et al. 2017).

These observations imply that good sleep and waking function require an optimal balance between sleep and wake duration. If finding the right sleep-wake balance is indeed essential for obtaining good quality sleep and waking function, then a number of questions emerge. What is 'normal/optimal' sleep duration and how to assess sufficiency of sleep on an individual basis? In this context, individual differences in sleep need and changes in sleep need across the adult life span may be considered.

Whether and how specific sleep stages predict the quality of wakefulness or brain function, i.e. cognition, has been investigated in young and older participants. In a comprehensive review of the literature addressing this question, it was concluded that a specific contribution of a specific sleep stage to cognition has not been firmly established (Scullin and Bliwise 2015). In one recent study, the association between

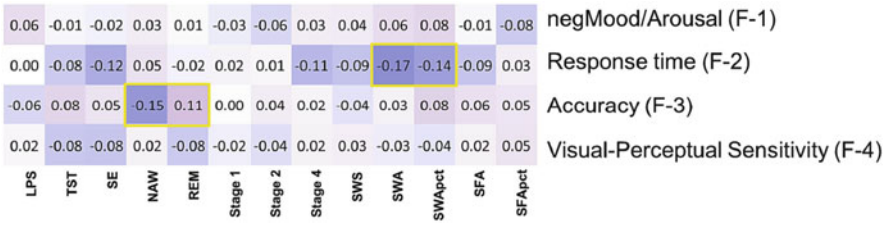

Fig. 3 Contribution of polysomnographically determined sleep variables to waking performance. Performance factors were derived from a factor analysis of performance measures. Colour coding represents Kendall's correlation coefficient, after controlling for sex and age. Note the negative correlation between SWA measures and response time, i.e. more SWA implies faster response times. A number of awakenings are negatively and REM sleep is positively correlated with accuracy. Modified from Della Monica et al. (2018)

nocturnal sleep and waking function was quantified across the healthy adult life span by an extensive battery of subjective and objective measures. After a factor analysis of the waking performance measures, it was found that SWS relates to a latent factor labelled 'Speed' of performance and REM sleep to 'Accuracy'. Importantly, sleep continuity was found to be the strongest predictor of 'Accuracy', which contains elements of executive function and working memory performance (Della Monica et al. 2018) (see Fig. 3).

Several observational studies have focused on contributions of specific aspects of sleep to other aspects of waking/brain function such as the association between sleep spindles and memory consolidation (Lafortune et al. 2014) and slow-wave sleep and metabolic clearance (e.g. Ju et al. 2018; Hladky and Barrand 2017). In the specific contexts of these studies, evidence for the contribution of slow-wave sleep, sleep spindles, REM sleep and sleep continuity to brain function has been reported although the magnitude of these effects and relative importance of various aspects of sleep remains to be established.

2.6.2 Interventional Studies

Interventional studies may provide more definitive insights into the relation between sleep and waking function. Acute total sleep deprivation, selective disruption of SWS and chronic sleep restriction all lead to an increase in subjective sleepiness and a reduction in objectively or subjectively assessed latency to sleep onset, measured at either habitual bedtime or during the daytime in the multiple sleep latency test (Carskadon and Dement 1987; Dijk et al. 2010a; Lo et al. 2012). Many studies have investigated the effects of sleep loss on aspects of brain function beyond sleepiness. Most studies implemented acute total sleep deprivation, but some used chronic partial sleep deprivation or selective disruption of SWS or sleep continuity (Lowe et al. 2017; Lo et al. 2012; Skorucak et al. 2018; Groeger et al. 2014). The most consistent finding is that sleep loss leads to impairment of vigilant attention. Many other aspects of waking performance are also affected. These include working memory, executive function, etc. Several studies have reported effects on memory

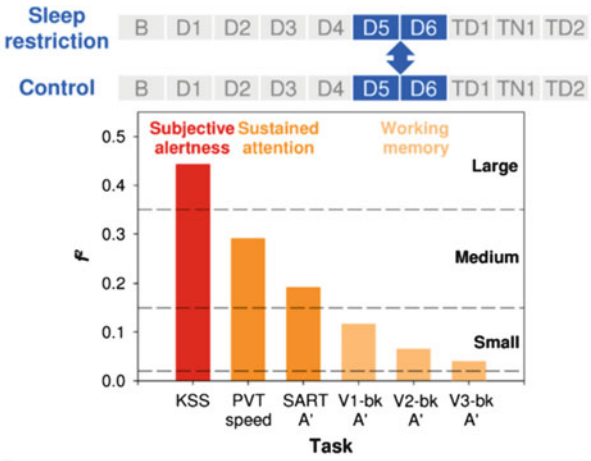

Fig. 4 Effects on 1 week of sleep restriction (6 h time in bed) on the Karolinska sleepiness scale (KSS), the 10% slowest reaction times on the psychomotor vigilance task (PVT), accuracy on the sustained attention to response task (SART) and accuracy of the verbal 1-, 2-, and 3-back. Modified from Lo et al. (2012)

consolidation as well. Repeated partial sleep deprivation studies have established that there is a progressive deterioration of waking performance and in particular of sustained attention suggesting that adaptation to sleep restriction does not occur (Van Dongen et al. 2003; Lo et al. 2012). It should be noted that repeated partial sleep deprivation does not lead to a large deficit in SWS but primarily to a deficit in REM sleep and N2, implying that the cognitive deficits cannot be attributed to SWS, but should be attributed to TST or REM sleep (Skorucak et al. 2018). It has been hypothesised that the cognitive deficits of sleep restriction were related to extension of the wake period beyond 16 h (Van Dongen et al. 2003), but this hypothesis was dismissed in a forced desynchrony study in which sleep-wake ratio was manipulated within 'days' shorter than 20 h. Despite the fact that wake episodes were never longer than 16 h, increasing the wake-sleep ratio nevertheless led to deficits in vigilant attention (McHill et al. 2018). This implies that it is simply the balance between wake and sleep duration that determines waking function and not the absolute duration of wakefulness.

Few studies have simultaneously assessed multiple aspects of waking function but those studies that did have shown that higher cognitive functions are less affected than relatively simple functions (e.g. sustained attention on the PVT) (see Fig. 4). In fact, it appears that if the sleep-deprived brain is able to engage with a task, deficits are relatively small. However, at the same time, the self-reported effort markedly increases. This suggests that insufficient sleep, at least with the time span of a week or so, does not lead to a fundamental inability of the waking brain to function even when, for example, working memory tasks with a high executive load are to be performed (Lo et al. 2012). The brain primarily struggles to stay awake and allocates more effort to maintain performance. Increases in subjective sleepiness and objective sleepiness and measures of effort are among the first signs of experimentally induced insufficient sleep and are among the dependent variables with the largest effect sizes (Balkin et al. 2004; Groeger et al. 2014; Lo et al. 2012). One major limitation of

these studies is that assessment of higher brain function in a realistic context was often not implemented. The implication is that functions such as creativity, complex decision-making and planning may still be markedly affected by insufficient sleep.

2.6.3 Individual Differences in Sleep Need and Response to Sleep Loss

Habitual long and short sleepers of approximately the same age differ in sleep propensity and sleep need when we consider total sleep time as the relevant measure of sleep propensity. However, nocturnal sleep latencies are longer in long sleepers, and short sleepers show more signs of intrusion of sleepiness-related theta activity during wakefulness (Aeschbach et al. 1996, 2001). Apparently long and short sleepers differ in their 'preferred' or 'tolerated' level of sleepiness. Whether and how this relates to homeostatic aspects of sleep regulation or to the longer circadian biological night observed in long sleepers remain unclear (Aeschbach et al. 2003).

Ageing is a major determinant of sleep propensity. Self-reported sleep duration and polysomnographically assessed total sleep time decline with age while at the same time daytime sleepiness decreases (Roenneberg 2013; Dijk et al. 2010a; Akerstedt et al. 2018). The most parsimonious explanation for these observations is that sleep need, at least as measured by sleep propensity, declines with age (Skeldon et al. 2016). An age-related reduction in the maximum capacity for sleep and reduction in sleep propensity has been demonstrated convincingly in protocols in which older and young adults spent 16 h in bed and this for several days. Older people slept 1.5 h less than young adults (who slept 8.7 h) but nevertheless were less sleepy (Klerman and Dijk 2008). That this reduction in the TST doesn't just reflect a reduced capacity for sleep but also for sleep need is supported by interventional studies which demonstrate that in older people the detrimental effects of total acute and repeated partial sleep deprivation are much smaller than in young people (Adam et al. 2006; Landolt et al. 2012; Zitting et al. 2018; Schwarz et al. 2018). Observational studies have not always confirmed these observations (Wild et al. 2018).

Individual differences in the deterioration of waking performance in response to total sleep deprivation and repeated partial sleep deprivation are also observed when only young adults are considered (Van Dongen et al. 2004; Rupp et al. 2012).

Several genetic variants associated with individual variation in sleep duration, sleep timing and sleep structure have been identified (Doherty et al. 2018; Rhodes et al. 2018; Viola et al. 2007; Archer et al. 2018). How genetic variants may affect response to sleep manipulations and pharmacological agents for wake and sleep promotion has been reviewed elsewhere (Bachmann et al. 2012; Holst et al. 2014; Landolt et al. 2018).

2.7 Effects of Insufficient Sleep on Peripheral Physiology, Endocrinology and the Blood Transcriptome

Insufficient sleep not only affects brain function and waking performance but also peripheral systems. This has been assessed by monitoring physiology during recovery sleep from total or chronic partial sleep deprivation and during wakefulness

following insufficient sleep. Autonomic tone changes in response to sleep loss such that during recovery sleep, there is shift to parasympathetic dominance as reflected in measures of heart rate variability (Viola et al. 2008a). Several hormones respond to insufficient sleep such that testosterone is suppressed, and appetite-regulating hormones ghrelin and leptin are up- and downregulated, respectively (Hanlon and Van Cauter 2011). Several markers of immune function respond to insufficient sleep such that immune function appears impaired (Irwin and Opp 2017). Finally genome-wide assessment of transcripts in whole blood has shown that sleep loss leads to changes in transcripts implicated in chromatin modification, gene expression regulation, macromolecular metabolism and inflammatory, immune and stress responses (Moller-Levet et al. 2013). Some of these changes may explain why and how insufficient sleep leads to adverse health outcomes such as obesity.

2.8 Sleep Physiology and Sleep Homeostasis as a Target for Pharmacological and Non-pharmacological Therapeutics

2.8.1 Sleep Promotion

Improving sleep quality in general focuses on latency to sleep onset, total sleep time and sleep continuity (maintenance) aspects such as wake after sleep onset or specific aspects of sleep structure such as slow-wave sleep. Peripheral correlates of sleep quality are in general not considered as target for sleep improvement.

Increasing homeostatic sleep pressure can improve latency to sleep onset, sleep continuity and total sleep time within a given time in bed period. This can be accomplished by increasing wake duration prior to sleep or by increasing the intensity of wakefulness through either physical or maybe mental activity. Such an approach may be useful in ageing and insomnia since in these conditions, optimal homeostatic sleep pressure may not be achieved because of daytime napping or excessive time in bed (Cross et al. 2015). Indeed, the recommended treatment of insomnia, which is the complaint of difficulties initiating and maintaining sleep, is cognitive behavioural therapy, the main component of which is thought to be sleep restriction (Maurer et al. 2018). An alternative approach to increase homeostatic sleep pressure may be to pharmacologically target the molecular signalling pathways of sleep homeostasis. Emerging pathways are adenosine and prostaglandins (Holst and Landolt 2018; Urade 2017; Korkutata et al. 2019) although approved drugs for these targets are not yet available.

Available pharmacological approaches of insomnia may target wake after sleep onset or sleep latency, but in general these approaches do not target the (largely unknown) molecular signalling pathways of sleep homeostasis but instead focus on inhibiting mechanisms related to 'arousal' and 'wake promotion', e.g. GABAergic, histaminergic and orexinergic mechanisms (Landolt et al. 2018).

Since SWA/SWS is accurately regulated in acute sleep manipulation protocols, is often considered a key indicator of sleep homeostasis, shows a marked age-related decline and has been implicated in memory consolidation, it has been and remains a target for sleep promotion and improvement (Mander et al. 2017; Wilckens et al.

2018). Non-pharmacological approaches include exercise and neuromodulation (Kredlow et al. 2015; Wilckens et al. 2018). In one type of neuromodulation, acoustic stimuli are phase locked to spontaneous slow waves. This has been reported to enhance slow waves in young people, but not in older people (Garcia-Molina et al. 2018). Whether this enhancement improves subjective sleep quality and waking function has not been firmly established. Rocking stimulation has recently been reported to increase SWS, spindle density in SWS and memory consolidation in healthy young adults (Perrault et al. 2019).

Pharmacological enhancement of slow-wave sleep has been accomplished by compounds that have different mechanisms of action. Agonists of the extra-synaptic $GABA_A$ receptor such as gaboxadol, also known as THIP, reliably induce SWS and SWA in healthy participants at baseline, in a model of transient insomnia (traffic noise, Dijk et al. 2012), a model of sleep onset insomnia (Mathias et al. 2001), a circadian phase advance model (Walsh et al. 2007), older participants (Lancel et al. 2001) and insomnia patients (Lankford et al. 2008). Interestingly, the effects of gaboxadol on sleep are much stronger in women than in men (Dijk et al. 2010b; Ma et al. 2011; Roth et al. 2010).

These enhancements of SWS were accompanied by modest improvement in sleep continuity and subjective sleep quality and in one report an improvement of daytime sleepiness and waking performance (Walsh et al. 2008). Gaboxadol was not fully developed as a treatment for insomnia, but its unique action on $GABA_A$ receptors containing the delta subunit and its effects on sleep and the EEG remain intriguing.

The most commonly used drugs for the treatment of insomnia are allosteric modulators of the $GABA_A$ receptor. In general these drugs do have hypnotic effects, e.g. improve wake after sleep onset (WASO), but do not enhance SWS, although zolpidem can enhance visually scored SWS (Bettica et al. 2012). Spectral analysis of the sleep EEG has revealed that the effects of all $GABA_A$ receptor allosteric modulators lead to a very similar spectral profile with reductions in delta and theta activity and enhancement in sigma activity (Arbon et al. 2015; Brunner et al. 1991; Trachsel et al. 1990) (see Fig. 5). This profile is very different from the spectral changes induced by physiological enhancement of homeostatic sleep pressure through sleep deprivation. The increase in visually scored SWS which is sometimes reported following zolpidem administration appears to be related to an increase in activity in very low-frequency slow waves (Landolt et al. 2000).

The hypnotic and EEG effects of $GABA_A$ receptor allosteric modulators can be separated, i.e. they are mediated by different receptor systems, and the rich variety of $GABA_A$ receptors remains a target for the pharmacological improvement of sleep (Wisden et al. 2017). In addition to $GABA_A$, $GABA_B$ receptors also appear to be involved in sleep regulation. $GABA_B$ receptors mediate some of the effects of gamma-hydroxybutyrate (GHB) and its sodium salt: sodium oxybate (SO). SO is the current first-line treatment of excessive daytime sleepiness and cataplexy in narcolepsy type 1. GHB induces SWS (Van Cauter et al. 1997; Dornbierer et al. 2019) and sleep onset REM periods (Vienne et al. 2012) and has been reported to improve performance (Walsh et al. 2010).

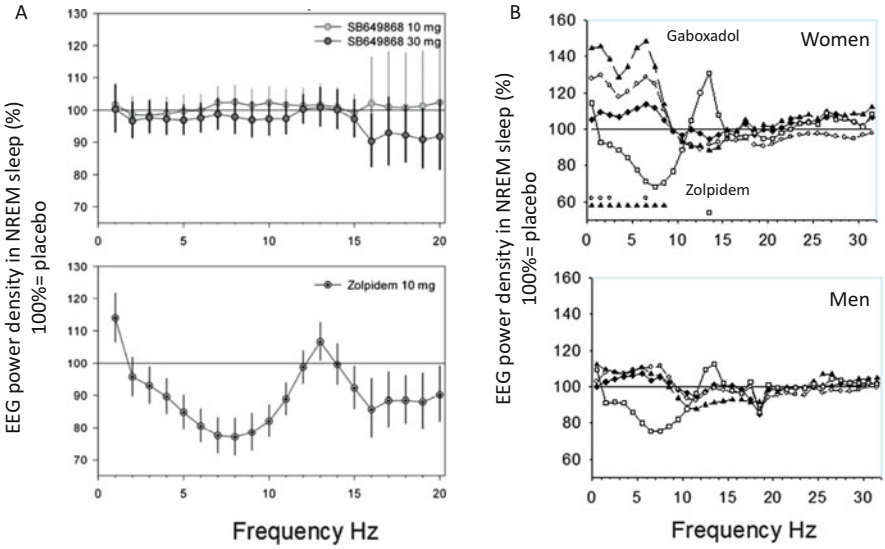

Fig. 5 (**a**) Effects of zolpidem and a dual orexin antagonist (SB-649868) on EEG power spectra in NREM sleep (modified from Bettica et al. 2012). (**b**) Sex differences in the effects of zolpidem (10 mg) and gaboxadol (5, 10, 15 mg) on EEG power spectra in NREM sleep. Modified from Dijk et al. (2010b)

Antagonists of serotonergic 5-HT_{2A} and histaminergic H_1 receptors the latter being widely used as nonprescription drugs for the treatment of sleep disturbances also enhance SWS. This maps on to the serotonergic and histaminergic pathways implicated in sleep-wake regulation generation (Landolt et al. 2018; Yu et al. 2018). The spectral profile of these effects is much more similar, although not identical, to the effects of sleep deprivation than the effects $GABA_A$ receptor allosteric modulators, i.e. these antagonists induce an increase in delta and theta activity (Dijk et al. 1989b; Landolt and Wehrle 2009). The pharmacological enhancement of SWS by 5-HT_{2A} antagonists is in general not accompanied by a shortening of sleep latency, an improvement in sleep continuity or a subjective sleep quality (Landolt et al. 1999). Alcohol is by many used as a sleep facilitator. It indeed hastens sleep onset but leads to more wakefulness in the second half of the sleep period, especially in older participants (Landolt et al. 1996). The effects of alcohol on EEG power spectra are different from those induced by $GABA_A$ allosteric modulators (Dijk et al. 1992a).

Sleep spindles are not a target in drug development for insomnia, even though several benzodiazepines and z-drugs enhance sleep spindle activity, and these changes have been related to changes in plasticity (Wisden et al. 2017).

Even though REM sleep deficits have been reported in insomnia (Baglioni et al. 2014) and in other conditions such as Alzheimer's disease (Winsky-Sommerer et al. 2018) and REM sleep is a positive predictor of subjective sleep quality and waking

performance (Della Monica et al. 2018), REM sleep enhancement does not appear to have been a target for pharmacological treatments. In fact REM sleep enhancement and reduced latencies to REM sleep observed after administration of orexin antagonists, e.g. (Bettica et al. 2012), are considered as an unwanted effect because of its potential link with narcolepsy and cataplexy (Jacobson et al. 2017).

Negative effects of hypnotics on waking performance after drug-enhanced sleep remain widespread despite continuing efforts to reduce these residual effects. For example, in one detailed analysis of the effects of zopiclone and eszopiclone, it was found that for some aspects of performance residual effects lasted as long as 11 h after dosing, i.e. until mid-late morning (Boyle et al. 2012a).

2.8.2 Wake Promotion

Extending sleep is one approach to reduce sleepiness caused by sleep restriction although this approach is obviously not realistic in idiopathic hypersomnolence (Baumann 2018).

Non-pharmacological approaches, other than extra sleep, to improve waking function include light exposure. Light has now been shown in a large number of experiments (both in humans and animals) to have direct alerting effects (Pachito et al. 2018; Viola et al. 2008b; Gaggioni et al. 2014). The photoreceptor and molecular and neuroanatomical signalling pathways have in part been elucidated (LeGates et al. 2014). Considering characteristics of light as an important non-pharmacological approach to improving alertness is relevant in view of the time we spend indoors where we are exposed primarily to artificial light.

Pharmacological approaches to improve alertness/wakefulness include caffeine (Wyatt et al. 2004) which through its adenosinergic action is thought to interact with sleep homeostatic mechanisms and indeed disrupts sleep (Clark and Landolt 2017). Although widely used, some of the effects of caffeine remain poorly understood. For example, and somewhat paradoxical, caffeine consumption may be associated with sleepiness (Wyatt et al. 2004). Patterns of caffeine consumption may suggest that it is primarily used to reduce sleep inertia and new delivery systems for this application have been developed (Newman et al. 2013).

Pharmacological approaches target the main wake-promoting systems such as the dopaminergic and histaminergic (H3) systems (Landolt et al. 2018). More recently the glutamatergic (AMPA receptor) system has been targeted for wake promotion. In experimental medicine type of conditions, these compounds have been shown to exert wake promotion as evidenced by longer latencies on the maintenance of wakefulness test or reduction of theta activity in the wake EEG (Boyle et al. 2012b; James et al. 2011; Iannone et al. 2010). At the same time little evidence for enhancement of cognition was observed. Furthermore, analyses of sleep following administration of compounds to promote wakefulness have documented ‘residual’ effects such as prolonged sleep latency or changes in sleep structure and the sleep EEG. Remarkably these effects were not observed after administration of modafinil (James et al. 2011; Bodenmann et al. 2012).

3 Circadian Rhythmicity: Sleep and Waking Performance

Circadian rhythmicity together with sleep homeostasis shapes the timing and structure of the sleep-wake cycle in young and older people and in men and women (Dijk and Czeisler 1995; Dijk et al. 1999; Wyatt et al. 1999; Santhi et al. 2016). Humans are a diurnal species, and in adult humans, sleep normally occurs at night and wakefulness during the day, although in modern industrialised societies with access to artificial light and the many social constraints it may be unclear where the day ends and the night begins (Skeldon et al. 2017; Walch et al. 2016). Sleep is not always monophasic, and daytime naps occur in normal and pathological conditions. Sleep timing can be measured against clock time, relative to the natural light-dark cycle and relative to preferred sleep timing, and imposed work schedules but also in relation to the many rhythmic circadian processes such as the hormones cortisol, melatonin, core body temperature, etc. (Dijk and Lockley 2002).

The timing and duration of sleep are among the most accessible characteristics of sleep, and dysregulation of these aspects may be related to circadian rhythm sleep disorders, insomnia, hypersomnia, etc. (see below). The two-process model of sleep regulation describes sleep timing as the result of the interaction of a circadian process and a homeostatic process (Daan et al. 1984; Borbély et al. 2016). The homeostatic aspect of sleep regulation relates to the contribution of sleep debt – as accrued during wakefulness and dissipating during sleep – to overall sleep propensity. The circadian process represents a clock-like intrinsically generated rhythm in sleep propensity. Sleep timing is also strongly influenced by social constraints such as work schedules and social obligations. Age-related and genetically determined differences in these processes and their interactions as well as psychological phenomena such as rumination and apprehension will shape individual differences in sleep-wake timing and the risk for sleep disturbances and sleep disorders (see Fig. 6).

3.1 Circadian Regulation of Sleep and Wakefulness

3.1.1 Circadian Rhythm of Sleep-Wake Propensity

The circadian process drives a rhythm in sleep-wake propensity and persists in the absence of sleep. The sleep-wake propensity rhythm is closely associated with the melatonin rhythm and the core body temperature rhythm. The waveform and timing of this sleep-wake propensity rhythm are at first glance somewhat paradoxical (Dijk and Czeisler 1994). Multiple protocols have established that in participants without sleep disturbances, the circadian drive for wakefulness increases during the waking day and reaches a maximum in the evening hours. The zone of maximum circadian drive for wakefulness, located just before the nocturnal (9–11 p.m.) increase in plasma melatonin concentrations, has been referred to as the wake maintenance zone (Strogatz et al. 1987). This drive for wakefulness then dissipates rapidly after the rise of melatonin (see Fig. 7).

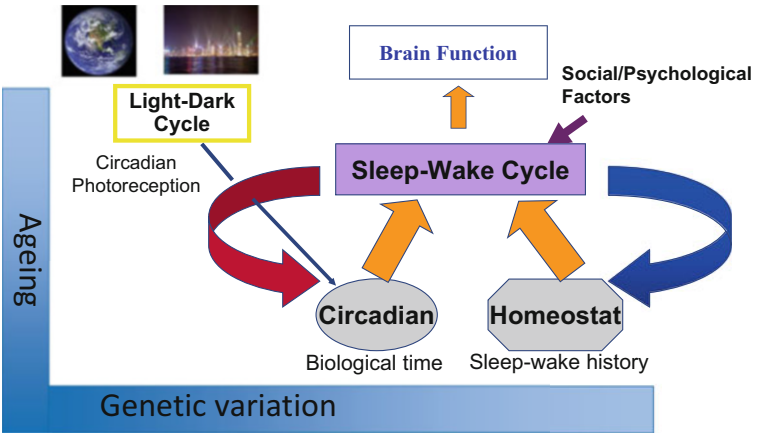

Fig. 6 Schematic representation of the interaction between circadian rhythmicity, sleep homeostasis and the light-dark cycle in the regulation of the sleep-wake cycle. Modified from Dijk and Lockley (2002)

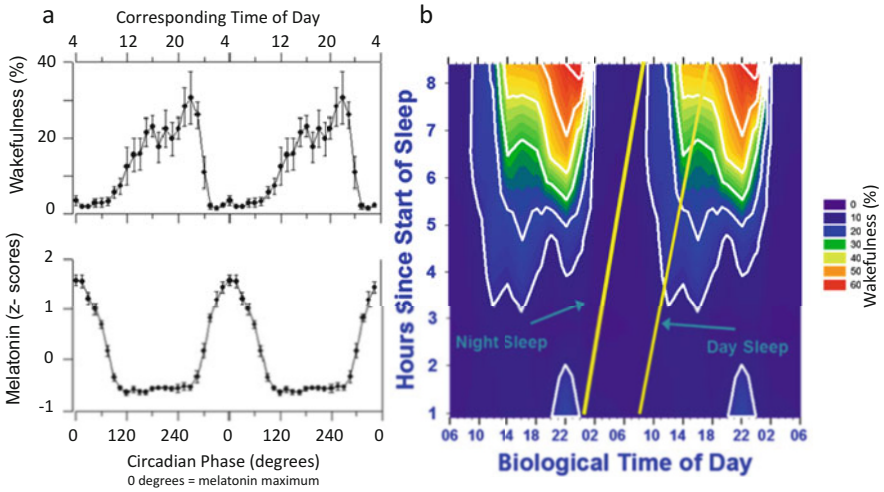

Fig. 7 Circadian and homeostatic regulation of sleep. (**a**) Association between wakefulness in sleep episode and the plasma melatonin rhythm. Modified from Dijk et al. (1997). (**b**) Sleep disruption (% wakefulness) as a function of hours since start of sleep episode and circadian phase. The two yellow trajectories represent a typical nocturnal and diurnal sleep episode. Modified from Dijk and Czeisler (1994)

The maximum circadian drive for sleep is located close to the nadir of the body temperature rhythm which in healthy participant occurs at around 4–6 a.m. and has been referred to as the sleep maintenance zone. When this circadian-driven sleep-

wake propensity rhythm is dysfunctional, a consolidated sleep-wake cycle is no longer observed (Dijk and von Schantz 2005; Czeisler and Gooley 2007).

3.1.2 Circadian Contribution to Sleep Structure, Sleep Continuity and the Sleep EEG

The circadian pacemaker actively promotes REM sleep such that even when expressed as a percentage of total sleep time, REM sleep propensity is maximal at around 2 h after the nadir of the core body temperature rhythm (Dijk and Czeisler 1995). The density of rapid eye movement is highest when sleep occurs in the evening hours, i.e. during the wake maintenance zone (Khalsa et al. 2002). Sleep continuity or sleep consolidation is an important determinant of sleep quality. The circadian process has a strong impact on this characteristic of sleep such that the duration of awakenings is much shorter during the biological night than during the biological day (Dijk et al. 2001).

The circadian pacemaker also modulates the EEG within sleep such that it actively promotes sleep spindle activity at night. The duration of sleep spindles is longer, their frequency is lower, and their amplitude is higher when sleep occurs at night (Wei et al. 1999). It has been hypothesised that this circadian modulation of sleep spindles may contribute to sleep consolidation (Dijk et al. 1997).

Slow waves are to a lesser extent modulated by circadian phase such that slow-wave activity is slightly lower and their slope is shallower when sleep occurs at night. The circadian modulation of the sleep and wake EEG, relative to the sleep-related modulation, is dependent on topography such that it is largest in occipital and smallest in frontal derivations (Lazar et al. 2015).

3.1.3 Intrinsic Circadian Period and Sleep Timing

Basic circadian rhythm research has established that the timing of the circadian clock relative to the 24 h cycle is determined by the strength (i.e. amplitude) of the light-dark cycle and the intrinsic, largely genetically determined, period of the circadian clock. Assessment of the intrinsic period of the circadian clock requires specialised protocols in which light input to the clock is absent (as in blind people) or distributed evenly across the circadian cycle in protocols in which the sleep-wake cycle is scheduled to a period several hours shorter or longer than the intrinsic circadian period and light levels during waking are very low (Duffy et al. 2011). These protocols have shown that on average, the intrinsic period is 24.15 h with a standard deviation of 0.2 h. Longer intrinsic periods are associated with later timing of the sleep-wake cycle, body temperature cycle, melatonin cycle and an evening-type diurnal preference and longer time in bed during weekends (Wright et al. 2001; Duffy et al. 2011; Lazar et al. 2013). Conversely, shorter periods are associated with earlier sleep timing, morning preference, etc.

Circadian rhythmicity is present not only in the suprachiasmatic nucleus (SCN) which hosts the master pacemaker driving the circadian sleep-wake propensity rhythm but also in the periphery. Intrinsic periods assessed through circadian reporter systems in cell cultures of fibroblasts have a weak association with SCN periods (Hasan et al. 2012).

3.1.4 Light Input

Under normal conditions, the circadian process is synchronised to the 24 h cycle, primarily by light. Exposure to light in the evening delays (slows down) the clock, i.e. clock-timed events like the rise of melatonin will occur later. Light in the morning will advance (speed up) the clock, and events such as the peak of the cortisol rhythm will occur earlier (Duffy and Wright 2005). The human circadian timing system is very sensitive to light, and ordinary room light exerts approximately 50% of the maximum effect of light (Zeitzer et al. 2000; Santhi et al. 2012). The discovery of melanopsin-expressing light-sensitive ganglion cells has drawn attention to the spectral composition of light as a determinant of the circadian effectiveness of light (Lucas et al. 2014). Blue light has been shown to be very effective, and the increasing blue light content of our LED home lighting and the blue light content of light emitted by the screens of our gadgets are now considered to be a determinant of sleep timing (Czeisler 2013; Gringras et al. 2015).

The timing of the circadian clock is determined by the overall 24-h pattern of light exposure, and sufficient exposure to daylight is now jeopardised because we spend most of our day indoors. Low levels of exposure to daylight, especially in the winter, will increase the delaying effects of artificial evening light.

3.1.5 Circadian Regulation of Waking Function

The circadian clock also modulates waking function. Thus many aspects of performance are impaired when performance is assessed in the early morning hours, at around the core temperature nadir, whereas in the evening hours, performance is at its maximum, even when homeostatic sleep pressure at these circadian phases is identical (Dijk et al. 1992b; Wyatt et al. 1999). Importantly, the effects of circadian phase on waking function interact with homeostatic sleep pressure. Deterioration of performance in the early morning is severe when it is combined with high homeostatic sleep pressure, either caused by acute sleep loss (Dijk et al. 1992b; Wyatt et al. 1999, 2004) or chronic sleep loss (Cohen et al. 2010b). These experiments have also shown that during the wake maintenance zone, the brain appears to be resilient against the effects of sleep loss. Brain correlates of the circadian and the wake duration-dependent deterioration of vigilant attention have been documented (Muto et al. 2016).

Although circadian misalignment affects many aspects of performance, effects are strongest for sleepiness, vigilant attention and effort (Santhi et al. 2016) although others have emphasised that the circadian system may significantly modulate aspects of higher cognitive function as well (Burke et al. 2015b).

3.1.6 Circadian Aspects of Sleep Disorders

The role of the circadian timing system in sleep disorders is well recognised. Circadian rhythm sleep-wake disorders are a separate diagnostic category in both the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and the *International Classification of Sleep Disorders, Third Edition*. These disorders include delayed, advanced, irregular, non-24-h, shift work and jet lag disorders. Causes of all of these disorders may be intrinsic, environmental or

behavioural and social, e.g. work schedules. The contribution of the circadian timing system to sleep disturbances in shift work and jet lag is obvious and in essence is caused by inertia of the circadian pacemaker. The circadian clock takes longer to shift than the acute displacement of the sleep-wake schedule imposed by either shift work or rapid travel across time zones. As a consequence people attempt to sleep during the biological day and to be awake and work during the biological night.

3.1.7 External Factors: Modern Light Exposure Patterns as an Environmental and Lifestyle Factor Contributing to Sleep-Wake Disturbances

Reduced or inappropriate light exposure or changes in light input pathways to the clock are obvious putative mechanisms of circadian sleep-wake disorders. Indeed, the contribution of the circadian timing system to the non-24-h sleep-wake disorders often observed in the blind is now well documented with 63% of blind individuals displaying circadian rhythms which are not appropriately synchronised to the 24-h day (Flynn-Evans et al. 2014). Inadequate or inappropriate light exposure, such as excessive evening light, may contribute to delayed sleep and evidence for this is now emerging. Indeed exposure to ordinary room light in the evening has been shown to suppress melatonin and sleepiness, delay bedtime and prolong sleep latency (Gooley et al. 2011; Santhi et al. 2012). Abnormal light exposure patterns are observed in delayed sleep-wake disorders (Van der Maren et al. 2018; Wilson et al. 2018). Furthermore individual differences in the circadian sensitivity to light are emerging (Santhi et al. 2012) and increased sensitivity to light may be a characteristic of delayed sleep-wake phase syndrome (DSPS) (Watson et al. 2018).

A major roadblock in the full exploration of the contribution of light exposure to circadian sleep-wake disturbances is the lack of adequate and acceptable longitudinal sensing systems for the intensity and spectral composition of retinal light exposure. Nevertheless, some studies combining light exposure measurements and mathematical modelling thereof have already shown that light exposure is a good predictor of circadian phase (Woelders et al. 2017).

3.1.8 Intrinsic Factors: Genetic Variants and Differences in Circadian Period Contributing to Sleep-Wake Disturbances

Genetic Variants

Evidence for the involvement of circadian rhythmicity in sleep timing abnormalities may be derived from the various polymorphisms and mutations in genes which are part of the molecular machinery generating circadian rhythms. Variations in the period genes have been associated with familial advanced sleep phase syndrome and DSPS. Some of these mutations and polymorphisms have been shown to shorten or lengthen circadian period when introduced in animal or cell culture models (Shi et al. 2017). Maybe somewhat surprising, other clock gene variants do not seem to affect circadian period even though they associate with variations in sleep timing (see below). Many clock gene variants associate with variation in diurnal preference (Kalmbach et al. 2017; Jones et al. 2016; Lane et al. 2016), and extremes of diurnal

preferences may translate to circadian sleep timing disorders. The effects of circadian variants to aspects of sleep other than its timing remain poorly characterised. It is of interest that several studies have now shown that circadian variants not only affect sleep timing but also sleep structure. For example, variants of the period genes are associated with differences in N3, i.e. slow-wave sleep (Hasan et al. 2014; Archer et al. 2018; Chang et al. 2016; Dijk and Archer 2010).

Circadian Period

Direct evidence for a contribution of *intrinsic* circadian factors such as abnormally long or short intrinsic circadian periods to circadian sleep-wake disorders is growing. Assessments of intrinsic circadian period in sleep disorders are rare, but it has been reported that circadian period is longer in DSPS and non-24-h sleep-wake disorder (Micic et al. 2016). It is often implied that developmental and age-related changes in circadian period contribute to late sleep timing in adolescence and early sleep timing in old age, but there is no solid evidence that the intrinsic circadian periods change with age (Dijk et al. 2000; Crowley et al. 2018; Skeldon et al. 2016). However, differences in circadian period as small as a few minutes may lead to substantial difference in entrained phase (Wright et al. 2005), and few studies with the statistical power to detect these small differences have been conducted. One example of small differences in circadian period concerns sex differences with circadian period in women being approximately 6 min shorter than in men (Duffy et al. 2011). This sex difference in intrinsic period may explain the earlier preferred timing of bedtime relative to clock time in women (Diurnal preference) and the earlier timing of the melatonin and core body temperature rhythm relative to sleep in women (Cain et al. 2010).

Circadian Phase

Indirect evidence for a contribution of the circadian timing system to variation in sleep timing stems from the observed associations between the timing of the melatonin rhythm and the timing of sleep in people without sleep timing complaints and in DSPS (Archer et al. 2008). Although this association implies that later timing of the melatonin rhythm may lead to later sleep timing, it cannot be excluded that the later sleep timing and associated light exposure lead to the delay of the melatonin rhythm. Recent data show that the intrinsic timing of the melatonin rhythm, as assessed by the dim light melatonin onset, is not delayed in almost half of DSPD patients (Murray et al. 2017).

The circadian timing system may also contribute to non-circadian sleep disorders. Insomnia with the prominent and persistent symptoms of difficulties initiating and maintaining sleep is in general not considered a circadian sleep disorder. Yet excessive strength of the evening wake maintenance zone or reduced circadian promotion of sleep during the night may contribute to these symptoms. Recently it was reported that in 10–22% of insomnia patients, the timing of sleep relative to the melatonin rhythm is abnormal such that sleep is attempted to be initiated at an early ‘melatonin time’ (Flynn-Evans et al. 2017).

3.1.9 Circadian Approaches to Treatment of Sleep-Wake Disturbances

In cases in which the cause of sleep-wake disturbances is clearly circadian, such as in jet lag disorder or non-24-h sleep-wake disorders in the blind, treatments are typically directed at the circadian timing system. Currently, abnormal timing of the circadian sleep-wake propensity rhythm may be corrected by either timed light exposure and light avoidance or administration of melatonin.

Light Treatment

Effects of time light exposure have been most extensively investigated in DSPS. Exposure to bright light in the morning, sometimes combined with instructions to avoid light in the evening, which theoretically should advance the sleep propensity rhythm, has been shown to be effective in DSPS (Richardson et al. 2018; Auger et al. 2015a, b). Optimisation of light treatment will require further quantitative understanding of the effects of light exposure patterns on the phase and amplitude of the circadian sleep-wake propensity rhythm. Current models for the effects of light do neither account for the spectral composition of light or the effects of prior light history on the sensitivity to light. Successful implementation of light therapy may also require assessment of circadian phase because effects of light depend on circadian phase, and, in some situation, like jet lag, circadian phase is not easily predicted. Light treatment also requires light delivery or light input manipulation systems that are easy to use and acceptable to users. Recent light treatment approaches have focused on reducing the blue light content of light to which the retina is exposed (Zerbini et al. 2018), and further development of methods by which the 24-h light exposure pattern, at the work place and at home, can be manipulated is a promising avenue for the treatment of some circadian rhythm sleep-wake disorders.

Development of novel therapeutics focusing on the light input pathway to the circadian system could target the anatomical and molecular pathways involved in entrainment.

Melatonin Therapy

Melatonin therapy has been successfully implemented in circadian rhythm sleep-wake disorders (Auger et al. 2015a, b) although the need for more research is recognised (Auger et al. 2015a, b). Melatonin is in the first instance an output of the circadian timing system. Its synthesis in the pineal is driven by sympathetic input, the rhythmicity of which is driven by the SCN such that in both nocturnal and diurnal species plasma melatonin concentrations are high during the biologically night and low during the biological day. This rhythm persists in constant darkness, but light at night suppresses melatonin. Melatonin administration leads to an increase in sleep propensity and shift of the sleep propensity rhythm, when it is administered when endogenous levels are low. This has been demonstrated in forced desynchrony protocols (Wyatt et al. 2006) and daytime sleep experiments (Rajaratnam et al. 2004) in participants without melatonin deficiency or sleep timing complaints. This effect is commonly referred to as the direct sleep-facilitating effect of melatonin. Melatonin can also induce a change in the timing of the endogenous

phase of rhythms driven by the SCN. Some of these phase markers include the cortisol, core body temperature and endogenous melatonin rhythm (Rajaratnam et al. 2003). The direction of the shift depends on the endogenous circadian phase at which melatonin is administered (Lewy et al. 1998). Circadian rhythms will be advanced when melatonin is administered several hours before the endogenous rise of melatonin, although the optimal timing has not been explored in great detail. Evidence for melatonin's effectiveness in delaying endogenous circadian rhythms is more limited. The phase-advancing effects of melatonin have been successfully exploited in several disorders such as DSPS (Sletten et al. 2018). Melatonin is also used to treat sleep disturbances in developmental disorders such as autism (Gringras et al. 2017). In all of these conditions, the largest effects are observed for latency to sleep onset. The effectiveness of melatonin in these conditions may be related to a combination of its direct sleep-facilitating and phase-shifting effects. Compared to allosteric modulators of the $GABA_A$ receptor, melatonin has very minor effects on slow-wave activity and EEG power spectra (Arbon et al. 2015).

Daily administration of melatonin can entrain non-synchronised rhythms, such as observed in the blind, to the 24 h day (Lockley et al. 2000). Melatonin treatment has also been advocated for the treatment of insomnia and in particular insomnia in older people (Lemoine and Zisapel 2012). The rationale for this approach is that endogenous melatonin levels may be too low in this particular patient group. The evidence for melatonin deficiency in insomnia is however rather limited although timing of melatonin may be abnormal in insomnia (see above).

Efforts have been made to optimise the dose of melatonin as well as the kinetics by, for example, slow-release preparations for oral or dermal delivery (Lemoine and Zisapel 2012; Aeschbach et al. 2009).

Effects of melatonin are mediated by M1 and M2 melatonin receptors which are abundant in the SCN but also in other brain areas. Melatonin receptor agonists have been developed for the treatment of insomnia (ramelteon) (Liu and Wang 2012) and non-24 h sleep-wake disorders (tasimelteon) (Lockley et al. 2015). Whether these agonists which have been approved are more effective than melatonin itself has not been investigated.

Further development of the melatonin-based treatment of sleep-wake disorders may benefit from new methods to assess endogenous circadian phase, which now requires collection of multiple samples under carefully controlled conditions. Several promising approaches based on analyses of the blood transcriptome have recently been developed (Laing et al. 2017; Wittenbrink et al. 2018).

3.1.10 Other Circadian Outputs and Novel Therapeutics for Sleep-Wake Disturbances

Further exploitation of the profound circadian influence on the sleep-wake propensity rhythm will require a better understanding of the neuroanatomical and molecular pathways by which the circadian system interacts with sleep executive systems generating sleep and wakefulness. An interesting example of interactions between sleep and circadian mechanisms relates to adenosinergic mechanisms. Caffeine, well known to affect sleep, also appears to affect the circadian timing system such that it

delays phase, lengthens circadian period (Burke et al. 2015a) and affects light sensitivity of the circadian timing system (van Diepen et al. 2014). Another example relates to orexin. The orexin system is under circadian control but is also affected by sleep deprivation (Deboer et al. 2004) and is implicated in sleep-wake regulation. Orexin antagonists have been successfully developed for the treatment of insomnia (Herring et al. 2018).

4 Novel Therapeutics and Sleep-Wake Regulation: Outlook

4.1 Continued Need and Opportunities

Given the high prevalence of sleep-wake disturbances and the imperfection of current treatments of these disturbances, efforts to develop novel therapeutics will continue and are warranted. These efforts will be informed by a better understanding of the multifaceted nature of sleep-wake regulation and disturbances thereof. The need for novel therapeutics is likely to increase because of the continued high prevalence of shift work and associated sleep-wake disorders, demographic changes with more people living longer and the increase in the number of people living with dementia and associated disruption of sleep-wake cycles. The multidimensional phenomenology of sleep and wakefulness implies that the treatment of disorders of sleep and wakefulness, and the development of new sleep-wake therapeutics, continues to require the input from a variety of scientific disciplines ranging from molecular biology to clinical and cognitive psychology.

4.2 A More Comprehensive Phenomenology of Sleep and Sleep Disturbances

Understanding the subjective complaints about sleep quality or complaints of waking function attributed to poor sleep will remain a first point of entry for sleep medicine and the development of novel therapeutics. A better understanding of how sleep complaints relate to sleep and circadian physiology will require a more comprehensive phenomenology of healthy sleep and disturbed sleep. This extended phenomenology may open up new avenues for the development of novel therapeutics. Examples of this are already available. The complaint of not being able to fall asleep is common to insomnia and circadian rhythm sleep-wake disorders (delayed). The observation that insomnia patients experience difficulties sleeping irrespective of time of day, whereas in delayed or advanced sleep phase syndromes, there are times of day at which sleep-ability is normal, distinguishes the two disorders. Although this may now appear to be trivial, it is only the recognition of the importance of the circadian timing system in sleep-wake regulation that allowed for this distinction and development of specific treatments. Within this context it may be relevant to point out that in the treatment of circadian rhythm sleep-wake disorders, sleep remains the relevant outcome measure, but the target for the

pharmacological and non-pharmacological therapeutics is far removed from classical sleep neurotransmitter systems. By contrast, in insomnia, neurotransmitter systems directly involved in sleep-wake regulation and associated processes such as arousal remain the target. Early on in these programmes, sleep physiology measures such as latency to sleep onset and wake after sleep onset are primary outcome measures, even though in at least a sizable fraction of insomnia patients, physiologically determined total sleep time is not severely abnormal (Vgontzas et al. 2013), and the complaint appears to be more related to the persistent mentation in the presence of physiological sleep. A better understanding of the sleep experience or the absence thereof and new EEG measures that better capture the sleep experience are needed. Efforts in this direction are already underway and can be guided by a simple question: what is the relation between sleep physiology and the sleep experience?

No doubt the discovery of other novel therapeutics will be parsimonious and not informed by any biased approach. Examples of current parsimoniously discovered therapeutics include the wake-promoting compound modafinil. It is only now that the important role of the dopaminergic system in wake (and sleep) regulation is recognised, providing a rational basis for modafinil's effects.

4.3 Short-Term vs Long-Term Treatment and Consequences of Short and Long Sleep as a Risk Factor for Ill Health

It is understandable that approaches to the development of novel therapeutics are primarily targeting acute and ongoing complaints about sleep. Successful treatments of these complaints may not only resolve the acute complaints but also have long-term health implications. Epidemiological studies indeed show that, for example, the complaint of insomnia is associated with adverse physical and mental health outcomes such as depression in particular (Sivertsen et al. 2014). Population-based epidemiological studies also show that not only short sleep duration but also long self-reported sleep duration predict negative health outcomes (Jike et al. 2018). Whereas the sleep research field, in which the 'sleep as a recovery process' is the prevailing view, can easily envision pathways from short sleep to ill health, although even these remain poorly defined, the pathways from long sleep to ill health remain unclear. In fact, it currently remains uncertain whether long sleep is an early consequence of covert ill health or a cause. Whereas approaches to lengthen short sleep can include advocating lifestyle changes, no currently accepted policy for long sleep including excessive napping, which, for example, is highly prevalent in dementia, is available.

A major limitation of the currently available epidemiology is that the exposure assessment (sleep duration) is to the larger extent based on self-report. Limitations of self-reported sleep duration are considerable, in particular, because the reporting error appears to be correlated with health outcomes (Miller et al. 2015).

4.4 Symptom Based vs Disorder (Nosology) Based

Traditionally the development of therapeutics was nosology or disorder based, and the underlying assumption is that specific disorders have a specific aetiology which can be targeted. This approach may work well in cases in which the disease or disorder and its aetiology are clearly defined. However, many disorders may be rather heterogenous, symptoms may be common to several disorders, and disorders may be closely related. For example, insomnia patients may display several anxiety-related symptoms. In fact GWAS studies of insomnia show that the genetic associations with insomnia and anxiety overlap to a considerable extent (Hammerschlag et al. 2017). Furthermore, insomnia disorder may consist of various subtypes with different aetiologies (Blanken et al. 2019). Thus insomnia with objectively reduced TST and insomnia without objectively reduced TST may have a different aetiology, different adverse consequences, etc. One approach to the development of therapeutics may be to target symptoms, e.g. anxiety, rather than a disorder, e.g. insomnia, and then target those insomnia patients who specifically suffer from anxiety symptoms. Precise and comprehensive phenomenology is obviously key to such an approach.

4.5 Sleep as a Whole-Body Phenomenon

Quantification of sleep often focuses on the brain. The EEG is a major source of information about the sleep process, but sleep is obviously much more than changed in neuronal firing patterns. Changes affecting both the brain and the body include temperature, cardiovascular, endocrine and many other variables. How peripheral physiology contributes to the sleep process and its recovery value remains somewhat under-investigated. For example, skin, body and brain temperatures are affected by sleep, and as early as 1967, Monroe reported body temperature during sleep to be higher in poor sleepers compared to good sleepers (Monroe 1967). Indeed, manipulating peripheral and central thermoregulatory processes have been shown to improve sleep in, for example, ageing (Te Lindert and Van Someren 2018). There is extensive epidemiology pointing to associations between sleep duration and obesity, and effects of sleep manipulation on appetite- and glucose-regulating hormones have been reported. Yet, relatively little is known about the effects of obesity or food intake on sleep. Future approaches to the development of novel therapeutics may exploit some of these peripheral phenomena to improve sleep for the brain and the body.

4.6 Interactions: Circadian Rhythmicity and Sleep-Wake History

The separate contribution of circadian rhythmicity and sleep-wake history (sleep homeostasis) to sleep propensity and waking functions is well recognised. However, the most important determinant of both sleep propensity and waking function is the

combined action of circadian rhythmicity and sleep homeostasis. Thus, waking performance at 6 a.m. close to the core body temperature nadir is not much impaired at all if the participant has had sufficient sleep prior to this time point. However, performance at this circadian phase is severely impaired when the participant is carrying an acute or chronic sleep debt. The implication for the development of novel therapeutics is that identification of the locus and mechanism of the interaction between circadian and homeostatic signals may offer new insights and targets. Some approaches are now emerging in preclinical research programmes in which local circadian clocks in arousal-related structures are manipulated and their effects on sleep-wake cycles are documented (Yu et al. 2014).

4.7 Monogenetic-Polygenetic, Monopharmacy vs Polypharmacy

Developing treatments of disorders of sleep and wakefulness necessarily implies the targeting of relevant circuits, receptor systems, etc. The ever more detailed description of the multitude of, for example, receptor subtypes offers opportunities for developing compounds with greater specificity for specific receptor subtypes. Likewise the ever more detailed description of the neuronal cell types regulating and contributing to specific aspects of sleep, e.g. sleep initiation vs REM sleep regulation, or EEG synchronisation. Such a specific targeted approach will be fruitful of specific receptor subtypes contributing to specific sleep disorders. This may be true in some cases, e.g. narcolepsy, even though even in this disorder, multiple neuromodulators have been implicated, but not in other cases. For example, it is unlikely that insomnia is caused by a deficiency in one particular $GABA_A$ receptor subtype. These states such as insomnia are likely to be associated with changes in constellations of biochemical signalling pathways. The implication is that a less specific treatment approach or drug development programme may be more effective.

4.8 The Sleep Environment

One defining aspect of sleep is partial disengagement from the environment, but the sleeper is not completely disconnected from its environment. Environmental influences on sleep and sleep disturbances may deserve more attention. Environmental variables that can be considered to be relevant include temperature, humidity, noise and light. With modern humans spending most of their time indoors, a closer look at the indoor environmental environment may be warranted. Sleep-wake cycles and their circadian regulation evolved in part as adaptation to environmental cycles related to the earth rotation around its axis. The light-dark cycle is one prominent example, but the natural darkness of the night is often hard to find in urban environments and the bedroom. Profound daily cycles in environmental temperature in the natural environment are to some extent mirrored in the circadian rhythm of body temperature which reaches a maximum during the later part of the day and a minimum close to dawn. Yet, temperature cycles in our home environments

including bedrooms are very different, and little is known about the potential impact of environmental temperature cycles on sleep-wake cycles and their quality.

4.9 Large-Scale Sleep Studies in the Home Environment

New developments in electronics, electrode technologies and signal analysis have enabled new recording and analyses approaches which have revealed novel aspects of sleep phenomenology. New recording technologies and new scoring approaches based on machine learning techniques using reduced montages will soon enable large-scale sleep studies in the home environment (Peake et al. 2018; Mikkelsen et al. 2019).

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