Journal of Cognitive and Behavioral Psychotherapies,
Vol. 13, No. 1a, July 2013, 133-170.

SLEEP-WAKE RHYTHMS AND COGNITION

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Abstract
In human beings, homeostatic and circadian sleep-wake regulatory processes are working together for the maintenance of sleep and wakefulness at appropriate times within the 24-hour light-dark cycle. The interaction between these processes also determines time-of-day modulations in sleepiness and alertness levels, and affects performance in a series of cognitive tasks. Besides, individuals differ in the synchronization of a great number of behaviors, ranging from preferred timing for sleep and wakefulness to habitual sleep duration or differences in sleep depth and sleep structure. Genetic factors have been shown to contribute substantially to inter-individual differences in most of these variables. Trait-like variability has also been suggested in the cerebral bases underlying cognitive effort under adverse circadian phase and sleep deprivation. The field of human sleep and chronobiology research has been shown suitable for translational research such that a multitude of therapeutic tools have been derived, which start to be recognized in sleep medicine and psychiatry. Regarding the presence of prominent inter-individual variability in sleep-wake behaviors and its impact on cognition and subjective well-being, individually tailored schemes might be more accurate, also for the prediction of treatment efficiency at the clinical level.

Keywords*:* sleep, circadian rhythms, inter-individual differences, cognitive performance

Introduction

Sleep and wakefulness are periodically occurring throughout the 24-hour light-dark cycle. Under normally entrained conditions, human beings are awake during the solar day and sleep during the dark phase at night. The quantity,

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quality, and timing of sleep and wakefulness is determined by the interaction between at least two oscillators, initially described in the two-process model of the circadian and homeostatic regulation of sleep and wakefulness (Borbély, 1982; Daan, Beersma, & Borbély, 1984). Importantly, both processes can majorly contribute to the modulation of cognitive behaviors throughout the 24-hour cycle (Dijk & von Schantz, 2005; Van Dongen & Dinges, 2005). The most frequently observed pattern consists in the maintenance of rather stable vigilance and performance levels throughout a classical 16-hour waking day, followed by a steep decrease once wakefulness is extended into the biological night, resulting in most detrimental performance levels at the end of the biological night, i.e. in the early morning hours. Some authors assume that task characteristics such as duration, cognitive load or the presence or absence of performance feedback can affect the way circadian and homeostatic mechanisms act on cognitive performance (Bonnet, 2005). More recently, it has also been suggested that such behavioral modulations can be mirrored at the cerebral level (e.g. Caldwell et al., 2005, Chuah, Venkatraman, Dinges, & Chee, 2006, Mu et al., 2005, Schmidt et al., 2009; Schmidt et al., 2012; Vandewalle et al., 2009). It is worth noting that there exist substantial inter-individual differences in the way we react to an imbalance between circadian and homeostatic processes, a situation provoked for example by total or partial sleep deprivation or by performing night or rotating shift work. In this perspective, recent evidence indicates that performance modulations associated with total sleep deprivation ranges from cognitive resistance to prominent performance impairment (Dorrian, Rogers, & Dinges, 2005). The factor age majorly contributes to the reaction induced by a sleep homeostatic challenge or to wakefulness at adverse circadian phases, as for instance being awake during the biological night. Different ages are associated with marked changes in the timing, consolidation, quality and quantity of sleep and wakefulness. Importantly, age-dependent modulations in circadian and homeostatic sleep-wake regulatory patterns might also result in a reduced susceptibility to the detrimental effects of sleep loss on neurobehavioral performance.

Independent of age, differential neurocognitive vulnerability to sleep deprivation can be considered as a stable trait and presents a robust neural basis (Van Dongen, Vitellaro, & Dinges, 2005; Van Dongen, Baynard, Maislin, & Dinges, 2004). Such inter-individual differences were observed for a variety of neurobehavioral tests ranging from basic psychomotor vigilance to more complex cognitive tasks, such as selective attention or memory functions (Chee & Chuah, 2008). Increasing evidence suggests a genetic contribution on the individual's vulnerability to cognitively perform under sleep homeostatic challenges or at adverse circadian phase (e.g. Bachmann, Klaus, et al., 2012; Bachmann, Klein, et al., 2012; Goel, Banks, Lin, Mignot, & Dinges, 2011; Goel, Banks, Mignot, & Dinges, 2009; Groeger et al., 2008; Retey et al., 2007; Retey et al., 2005; Viola et al., 2007).

In this review, we aim at describing the impact of sleep-wake cycles and the detrimental effects of an imbalance between its underlying regulation processes on cognition, its cerebral correlates as well as the presence of inter-individual differences in the ability to cognitively cope with sleep loss and wakefulness at adverse circadian phase. The review will close with a series of clinical interventions derived from sleep and circadian research, targeting on sleep-wake cycle consolidation and thereby potentially improving cognitive performance, mood and well-being.

Regulation of sleep and wakefulness: circadian and homeostatic processes

In the two-process model of sleep and wake regulation, circadian and homeostatic processes work in harmony or in opposition to each other in order to achieve consolidated states of sleep and wakefulness at appropriate times of the day (Figure 1; Borbely, 1982; Daan, et al., 1984). The circadian process represents a nearly 24-hour endogenous modulation in the propensity for sleep or wakefulness.

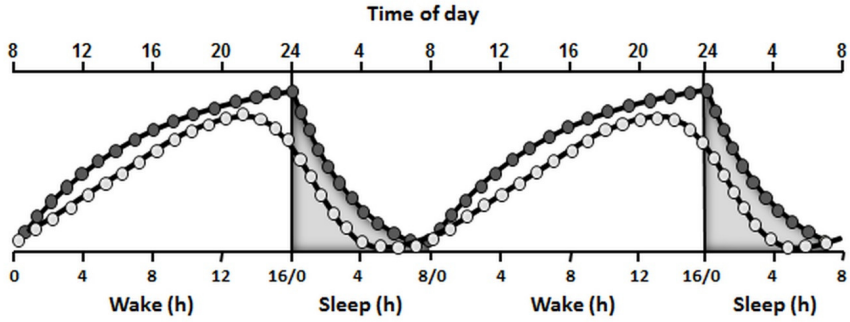

Figure 1. Schematic illustration of the two-process model of sleep-wake regulation (modified from Daan et al., 1984). The circadian process C (light grey) oscillates with a phase of nearly 24-hours independent of the prior sleep-wake history. Mainly reset by the light-dark-cycle, it promotes wakefulness and sleep under entrained conditions according to time of day. In contrast, the homeostatic process S (dark grey) increases with enduring wakefulness and declines during sleep relatively unaffected by the 24-hour cycle. In the end, the interaction of both processes determines the timing, the duration and the quality of sleep and wakefulness.

Under constant conditions, circadian rhythms start free-running with a period that deviates slightly from the environmental 24-hour light-dark cycle by which they are synchronized or entrained in nature. Disclosing genuine rhythmic

clock outputs requires strong control over all possible exogenous or endogenous cues in order to avoid their masking influence on the specific variables measured. Thus, ambient light, temperature, body position (semi-recumbent posture in bed) and food intake (hourly isocaloric snacks) are kept at constant levels while subjects must stay awake for more than 24 hours. Physiological and behavioural measurements are usually assessed at fixed time intervals. By tightly controlling and minimizing all rhythmic external masking factors, such protocols allow the quantification of the endogenous phase or amplitude of circadian rhythmicity.

Circadian regulation is driven by a small region in the anterior hypothalamus of the brain, the suprachiasmatic nucleus, defined as the circadian master clock. The process of entrainment is important, as it consists in the coupling of an endogenous rhythm to an external cycle, such as the light-dark cycle, with the consequence that both oscillations have the same frequency and thus enable the organism to adapt to and anticipate environmental changes (Cajochen, Chellappa, & Schmidt, 2010). As a result, the circadian clock actively gates sleep and wakefulness in synchrony with the light–dark cycle. In humans, the circadian rhythm of melatonin production by the pineal gland and of core body temperature are considered as good markers of endogenous circadian rhythmicity when collected under constant conditions. These markers are closely associated with the endogenous circadian component of the sleep-wake propensity rhythm (e.g. Cajochen, Krauchi, & Wirz-Justice, 2003), as well as with the observed circadian modulation in neurobehavioral performance (e.g. Dijk, Duffy, & Czeisler, 1992).

Homeostasis has been defined as "coordinated physiological processes which maintain most of the steady states in the organism" (Cannon, 1939, cited in Borbely & Achermann, 2005; p.405). Sleep homeostatic mechanisms promote sleep propensity in function of time spent awake (Borbely & Achermann, 2005). This process organizes the appropriate structure and duration of both sleep and wakefulness, relative to the prior history of these variables (Dijk & Franken, 2005). Relatively irrespective of time of day, sleep homeostatic markers, often referred to as sleep pressure, increase during wakefulness and decline during sleep, thereby providing a balance between time spent awake and time spent asleep. The time course of sleep homeostatic dissipation can be derived from electroencephalographic (EEG) slow wave activity (SWA, also called delta activity; Borbely & Achermann, 1999). SWA decreases exponentially in the course of sleep (Dijk & Czeisler, 1994, 1995). Low frequencies in waking EEG have also been used successfully to delineate the increase in homeostatic sleep pressure during the waking state (Aeschbach et al., 1997; Cajochen, Khalsa, Wyatt, Czeisler, & Dijk, 1999; Dumont, Macchi, Carrier, Lafrance, & Hebert, 1999). Homeostatic sleep pressure can therefore be considered as a sleep-promoting process that continuously accumulates with increasing time spent awake – concomitantly with a decrease in waking cognitive performance.

In the field of human chronobiology, several protocols have been developed to allow more fine-grained exploration of these processes. The forced desynchrony (FD) paradigm can be considered as the gold standard (Czeisler, Brown, Ronda, & Kronauer, 1985). In this protocol, a sleep-wake cycle being significantly longer or shorter than 24 hours (e.g. 28 hours instead of 24 hours) is adopted, leading to a desynchronisation between circadian rhythmicity and the sleep-wake cycle and therefore allowing the investigation of sleep and waking performance at virtually all circadian phases. This protocol in its classical form is time-consuming and requires temporal isolation units in which volunteers have to stay for a long time (generally 2 to 8 weeks). In contrast, constant routine (CR) protocols are more feasible since they allow the evaluation of circadian phase and amplitude during a relatively short stay in the laboratory (usually about 40 hours) while body posture, nutrition and light influence are kept constant. However, since a CR in its classic form involves sleep deprivation, it entails a gradually increasing level of homeostatic sleep pressure, which may also affect circadian phase position (Cajochen, Jewett, & Dijk, 2003). Alternatively, the circadian effect may be more clearly highlighted when the subject is exposed to ultra-short sleep-wake cycles, so that periods of sleep are equally distributed over the circadian cycle in order to keep the sleep homeostat at rather constant levels (Carskadon & Dement, 1975; Lavie, 1986). This procedure may allow researchers to investigate the time course of endogenous circadian sleep-wake propensity but does not permit an analysis of sleep structure during an entire night. Cajochen, Knoblauch, Krauchi, Renz, and Wirz-Justice (2001) combined such a "nap protocol", respecting the habitual ratio between sleep and wakefulness, with sleep deprivation under constant conditions. The combination of the two protocols allowed them to measure the effect of low versus high homeostatic sleep pressure levels at many circadian phases.

The application of such protocols revealed that circadian-based wake propensity is at its highest level during the early evening hours, when homeostatic sleep pressure is high, whereas circadian propensity for sleep reaches its maximum during the early morning, when homeostatic sleep pressure is low (Dijk & Czeisler, 1994). Sleeping at the wrong time throughout the 24-hour cycle might lead to less recuperative sleep and associated disproportional sleepiness during wakefulness. Likewise, sleep loss affects the quality of wakefulness, but not in a linear way, such that sleep deprivation is most detrimental for cognitive behaviors at the end of the biological night, when circadian-based sleep propensity is highest. Importantly, partial and total sleep loss, as well as sleep at the wrong time of day, is no longer an exception in our 24-hour society.

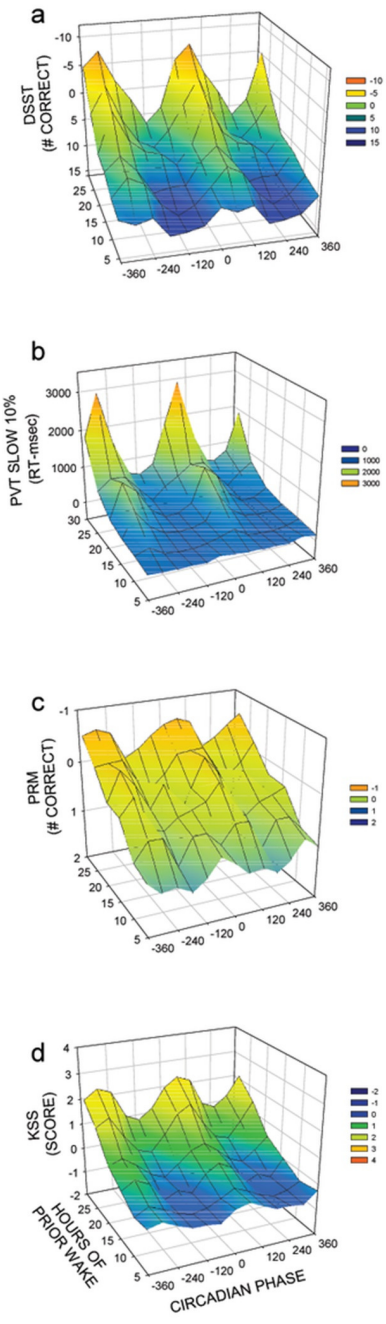

Figure 2. Circadian and homeostatic modulations in cognitive performance. The interaction between the duration of prior wakefulness (y-axis of each panel) and circadian phase as measured by plasma melatonin levels (x-axis of each panel, double-plotted) is highlighted (0 degrees corresponds to approximately 4 a.m. under entrained conditions). Modulation of selected neurobehavioral measures are depicted in the z-axis of each panel, with 0 corresponding to each subject's average value from the baseline. Higher values on the z-axis indicate higher levels of impairment. DSST refers to the number correct trials on Digit Symbol Substitution Task; PVT, the slowest 10% of reaction times on the Psychomotor Vigilance Task; PRM, the number correct trials on the Probed Recall Memory task; KSS, the rating on the Karolinska Sleepiness Scale (reprinted with permission from Wyatt et al., 2004).

Circadian and homeostatic regulation of cognitive performance

The impact of potential time-of-day variations on brain activity and cognitive performance has widely been ignored in cognitive psychology and neuropsychology, even though Ebbinghaus (1964/1885) already reported that learning of nonsense syllables is better in the morning than in the evening (Schmidt, Collette, Cajochen, & Peigneux, 2007).

The respective contributions of homeostatic sleep pressure and circadian rhythmicity on neurobehavioral performance measures were identified through FD and CR studies (Cajochen, Blatter, & Wallach, 2004; Cajochen, et al., 1999; Cajochen et al., 2004; Dijk, et al., 1992; Dijk & von Schantz, 2005; Graw, Krauchi, Knoblauch, Wirz-Justice, & Cajochen, 2004; Horowitz, Cade, Wolfe, & Czeisler, 2003; Johnson et al., 1992; Wyatt, Cajochen, Ritz-De Cecco, Czeisler, & Dijk, 2004; Wyatt, Ritz-De Cecco, Czeisler, & Dijk, 1999; Figure 2). These studies revealed that when the circadian contribution to performance is controlled, already short waking episodes can lead to significant performance deteriorations. Globally, performance decrements emerging from increasing homeostatic sleep pressure are counteracted by circadian wake-promotion during the biological day, allowing the achievement of appropriate neurobehavioral performance (Vandewalle & Schmidt, 2013). However, if wakefulness is extended into the biological night, the circadian signal promotes sleep, and cognitive performance is affected most strongly at the end of the night (Vandewalle & Schmidt, 2013). If wakefulness is then further extended into the biological day, performance stabilizes or even expresses a relative increase as compared to the preceding biological night. Importantly, the amplitude of the observed circadian modulation in performance depends on homeostatic sleep pressure (Dijk & Archer, 2009): when sleep pressure is low, the circadian variation in performance remains relatively small. However, when sleep pressure increases, the amplitude of the circadian modulation is higher and performance is markedly impaired, especially during the biological night (Dijk & Archer, 2009). Within the same perspective, when the circadian rhythm is out of phase with scheduled sleep and wakefulness, a situation encountered in shift work schedules, impairments in learning and cognitive performance can be detected even over the course of a normal 16 hour waking day (Wright, Hull, Hughes, Ronda, & Czeisler, 2006).

Intra- and inter-individual differences in sleep-wake regulation and its impact on cognitive performance

Prominent variability can exist in the synchronization of human behaviors, such as preferred sleep and wake timing or duration, the optimal time of day to perform cognitively demanding tasks, or the way we are able to cope with sleep deprivation at the physiological and cognitive level. As mentioned

above, the factor age can have a strong impact on our sleep-wake behavior. Within these broad age-based tendencies, there are substantial individual differences. Generally, the distribution of cognitive responses to sleep loss can range from no modulation at all ("cognitive resistance") to severe performance impairment for a given cognitive domain (Dorrian, et al., 2005). Here, we will shortly summarize some of the main sources underlying inter-individual differences in circadian and homeostatic regulation of sleep and wakefulness as well as its potential impact on cognitive performance (see also Table 1 for a summary).

Table 1. Overview of reported variables potentially contributing to cognitive vulnerability associated to circadian and homeostatic processes

	Affected cognitive domain	**References**
Age	Reduced susceptibility in vigilance under SD in older adults	Adam et al., 2006; Blatter et al., 2006; Duffy et al., 2009
Chronotype	Extreme chronotypes tend to differ in their diurnal variation of vigilance; inhibition tasks do not differ if test time is adapted to chronotype	Mongrain et al., 2008; Schmidt et al., 2009; Schmidt et al., 2012
PER3	Greater impairment in PER3$^{5/5}$ carriers during early morning hours under SD in several cognitive tests (especially working memory), during PSD no differences	Viola et al., 2007; Groeger et al., 2008; Goel et al., 2009; Lo et al., 2012
ADA	Greater impairment of G/A carriers in vigilance during SD	Bachmann et al., 2012
ADORA	Greater impairment of T/T carriers in vigilance during SR	Rupp et al., 2012
BDNF	Genotype-dependent modulation under rising/high sleep pressure in working memory	Bachmann et al., 2012
COMT	Efficacy of modafinil to counteract performance decline depends on genotype	Bodenmann et al., 2009; Bodenmann et al., 2009; Goel et al., 2011

Notes. SD=Sleep deprivation; PSD=partial sleep deprivation; SR=sleep restriction

Developmental differences in sleep-wake regulation and its impact on cognition

The process of aging significantly affects circadian and sleep variables. Children, university students and older adults for example have different time-of-day preferences for sleep and wakefulness (Hasher, Goldstein, & May, 2005). The nocturnal sleep consolidation reflects the maturation of intrinsic circadian and

homeostatic sleep-wake processes (see Jenni & LeBourgeois, 2006 for a review on sleep-wake behaviour and sleep regulation in children). Frequent night awakenings may occur when homeostatic and circadian processes are not aligned. Homeostatic and circadian processes seem not develop at the same rate. Hyperarousal and/or excessive crying may occur for example because circadian alertness is not yet opposed by homeostatic sleep pressure in the evening hours (Jenni & LeBourgeois, 2006). Evidence indicates that the dynamics of sleep homeostatic processes slow down in the course of childhood (i.e., sleep pressure accumulates more slowly with increasing age) enabling children to be awake for consolidated periods during the day with increasing age. The biological clock of adolescents has a markedly late circadian phase (Foster & Roenneberg, 2008) compared to younger children and older adults. The eveningness chronotype is predominant in this age group and delayed sleep phase syndrome is prevalent (7-16%; Pelayo, Thorpy, & Glovinsky, 1988). Differences in homeostatic and circadian processes have been associated with this phenomenon (Carskadon, 2011; Crowley, Acebo, & Carskadon, 2007; Hagenauer, Perryman, Lee, & Carskadon, 2009). In brief, the homeostatic sleep pressure built-up across the waking day has been shown to be longer in a more mature adolescents group as compared to a less mature group. This result indicates that more mature adolescents may find it easier to stay awake longer in the evening hours than the less mature (Jenni, Achermann, & Carskadon, 2005). Marked differences in the circadian system have also been observed compared to other age groups (Foster & Roenneberg, 2008). During adolescence, the circadian timing system undergoes a phase delay (e.g. Carskadon, Vieira, & Acebo, 1993). Andrade and colleagues (Andrade, Benedito-Silva, Domenice, Arnhold, & Menna-Barreto, 1993) observed in a longitudinal study that circadian phase was positively related to adolescent maturation, with more mature adolescents having later circadian phases. Other studies reported longer intrinsic circadian periods in adolescents as compared to adults, both in rats (McGinnis, Lumia, Tetel, Molenda-Figueira, & Possidente, 2007) and humans (see Carskadon, 2011 for a discussion). Importantly, late sleep timing in adolescents stays in conflict with socially desired early school schedules leading to the accumulation of sleep debt during school days (Wittmann, Dinich, Merrow, & Roenneberg, 2006). Late chronotypes, and thus most adolescents, show the largest differences in sleep timing between work/school and free days (Wittmann, et al., 2006). Compared to adults and the aged population, the impact of such sleep-wake characteristics on cognitive performance in adolescents remains poorly investigated to date. A study performed during normally entrained conditions revealed however that evening type adolescents performed better on cognitive tasks challenging fluid intelligence or executive functions during the evening hours, as compared to those tested in the morning hours (Goldstein, Hahn, Hasher, Wiprzycka, & Zelazo, 2007; Hahn et al., 2012).

A common feature of advanced age is the shift of habitual bedtimes and getting-up times to earlier hours (Carrier, Monk, Buysse, & Kupfer, 1997), which has been associated with an advance in circadian phase at the physiological level (Duffy & Czeisler, 2002; Duffy, Dijk, Hall, & Czeisler, 1999). Regarding sleep architecture, an age-related decline in the absolute level of slow wave sleep has been reported by several studies (e.g. Carrier, Land, Buysse, Kupfer, & Monk, 2001; Landolt, Dijk, Achermann, & Borbely, 1996; Munch et al., 2004; Smith, Karacan, & Yang, 1977). Getting older has also been associated with an amplitude reduction in circadian rhythm output markers, such as salivary melatonin or core body temperature (Duffy, Dijk, Klerman, & Czeisler, 1998; Munch et al., 2005). Concomitantly, sleep over the 24-hour cycle seems to be less affected by circadian time as compared to younger participants, indicating weaker wake promotion at the end of the biological day (Munch, et al., 2005), or weaker circadian-based sleep promotion at the end of the biological night (Dijk & Duffy, 1999; Duffy, et al., 1998). It remains still controversial to what extent these age-related modulations can be attributed to changes in the circadian signal per se, or to differences in its transduction to other central and peripheral regions (Monk & Kupfer, 2000). Beside apparent differences in circadian markers, less steep homeostatic sleep pressure dissipation throughout the night has been observed in older adults after sleep deprivation (Dijk, Beersma, & van den Hoofdakker, 1989; Munch, et al., 2004). It has been hypothesized that the age-related deterioration in sleep continuity is related to a reduction in NREM sleep consolidation, and primarily reflects a reduction in sleep need (Klerman & Dijk, 2008).

Importantly, as a potential by-product of shallower built-up of homeostatic sleep pressure and reduced circadian modulation, older adults also present a reduced neurobehavioral susceptibility to the detrimental effects of sleep loss, especially during the biological night. As a consequence, under sleep deprivation conditions, the classically observed age-related slowing down in the reaction times during a vigilance task is abolished at night such that younger adults reach the level of older adults once exposed to challenging sleep homeostatic pressure and/or circadian phase (e.g. Adam, Retey, Khatami, & Landolt, 2006; Blatter et al., 2006; Duffy, Willson, Wang, & Czeisler, 2009). It is thus assumed that older adults tolerate sleep deprivation better than healthy young adults do (Duffy, et al., 2009).

Trait-like inter-individual differences in the sleep-wake cycle

Within a given age-range, differential neurocognitive vulnerability to sleep deprivation is domain-specific and can be considered as a stable trait (Van Dongen, et al., 2005; Van Dongen, et al., 2004). From a conceptual point of view, it has been shown that the two-process model of sleep-wake regulation better represents performance modulation when the parameters of the model are systematically adjusted to account for an individual's initial state and unknown trait characteristics (Rajaraman, Gribok, Wesensten, Balkin, & Reifman, 2008).

At the behavioral level, trait-like individual variability in response to experimentally induced sleep deprivation has been shown to cluster around three different neurobehavioral dimensions: subjective sleepiness, cognitive processing and behavioral alertness, as investigated by a sustained attention task (Van Dongen, et al., 2004). Such multiple dimensions led researchers to assume that distinct neurocognitive subsystems may regulate different aspects of the cognitive effects of sleep deprivation and support the hypothesis that the course of task performance is significantly affected by the specific cognitive domain investigated. Recent data indicate that humans' susceptibility to sleep deprivation has a genetic basis. In the following sections, we will describe phenotypic and genotypic traits which have been shown to affect our sleep-wake behavior, and by consequence the ability to cognitively cope with sleep loss or wakefulness at adverse circadian phase.

Phenotypic traits in the human sleep-wake behavior

The existence of prominent inter-individual variations in the circadian timing system has a marked impact on the daily temporal organization of human behaviors. A series of studies observed an advanced sleep schedule (Hidalgo et al., 2002; Roenneberg, Wirz-Justice, & Merrow, 2003; Vink, Groot, Kerkhof, & Boomsma, 2001) and an earlier circadian phase (Baehr, Revelle, & Eastman, 2000) in women compared to men. Likewise, women also show greater morningness tendencies on chronotype scales (Hidalgo, et al., 2002; Roenneberg, et al., 2003). Some sleep studies have noted more slow-wave sleep in women compared with men (Carrier, Monk, Buysse, & Kupfer, 1997), and more spectral power in NREM delta, theta, and sigma bands in women (e.g. Carrier, Land, Buysse, Kupfer, & Monk, 2001; Dijk, Beersma, & Bloem, 1989). Morningness vs. eveningness represents a substantial source of inter-individual variation: "… extreme 'larks' wake up when extreme 'owls' fall asleep" (Roenneberg, Wirz-Justice, & Merrow, 2003, p. 80). Differences in timing preference are expressed in favorite periods of diurnal activity, such as working hours, and in specific sleep habits (Taillard, Philip, Coste, Sagaspe, & Bioulac, 2003) that reflect an individual's particular chronotype. At one end of the continuum the extreme morning types (i.e., the "larks") are located, who show a marked preference for waking up very early, and find it difficult to remain awake in the late evening hours. At the opposite are the extreme evening types (i.e., the "owls") who prefer to go to bed in the late hours of the night and often find it extremely difficult to get up in the morning. The morningness-eveningness chronotype can be evaluated using self-report questionnaires, the most popular of which are the Morningness-Eveningness Questionnaire (MEQ; Horne & Östberg, 1976) and the Munich Chronotype Questionnaire (MCTQ; Roenneberg, et al., 2003). Of course, the timing of self-selected sleep is multifactorial. In addition to genetic dispositions, it includes for example work schedules and social factors influencing decisions about bedtime as well as differences in light exposure.

Evening types tend to vary considerably in their bedtime, waking-up time and sleep length (Kerkhof, 1985; Monk, Petrie, Hayes, & Kupfer, 1994; Taillard, Philip, & Bioulac, 1999), resulting in more irregular sleep-wake schedules compared to morning types (Monk, et al., 1994). As already mentioned, late chronotypes show the greatest differences in sleep timing between work and free days (Wittmann, et al., 2006). It has been shown that, when a sleep-wake schedule is imposed as required by working hours, young evening types are sleepier during the day than morning types, especially in the morning hours (Volk, Dyroff, Georgi, & Pflug, 1994). Furthermore, on workdays, sleep inertia (i.e. "a period of drowsiness and impaired performance after the transition from sleep to waking"; Hofer-Tinguely et al., 2005) is more pronounced in evening than in morning types, whereas on free days, sleep inertia is independent of chronotype (Roenneberg, et al., 2003).

From a circadian perspective, extreme chronotypes are "phase-shifted", that is, the peaks and troughs of their physiological circadian markers occur earlier (phase advance, morning types) or later (phase delay, evening types) in relation to the external clock time (Baehr, Revelle, & Eastman, 2000; Bailey & Heitkemper, 2001; Duffy, et al., 1999; Duffy, Rimmer, & Czeisler, 2001; Kerkhof & Van Dongen, 1996; Mongrain, Lavoie, Selmaoui, Paquet, & Dumont, 2004). Differences in the intrinsic period of the circadian oscillator may account for chronotype-dependent phase and phase angle differences (Kerkhof, 1985). This would imply that morning types are characterized by short periods and evening types by long periods, a hypothesis supported by data collected during a forced desynchrony protocol, revealing that subjects with shorter intrinsic periods rate themselves as more morning-like and tend to have earlier circadian phase and wake times (Duffy et al., 2001).

An increasing amount of evidence suggests that chronotypes also differ in their homeostatic sleep regulation. Kerkhof's group was the first to observe that, relative to evening types, morning types tend to have a larger decrease in delta activity through the first sleep cycles of the night (Kerkhof, 1991). When Mongrain and colleagues tested their subjects in a context free from major socio-professional constraints, they also found evidence that chronotypes differ in homeostatic sleep regulation during normal day-night conditions, with morning types showing a faster dissipation rate of homeostatic sleep pressure throughout the night (Mongrain, Carrier, & Dumont, 2005). Interestingly, morning types also tend to begin their sleep episode with higher SWA levels (Mongrain, Carrier, & Dumont, 2006a, 2006b). It has been hypothesized that a higher homeostatic response to increasing time spent awake is the consequence of a faster accumulation rate of sleep pressure during wakefulness. This assumption was strengthened by data from Taillard (Taillard, et al., 2003), who observed chronotype-dependent differences in the kinetics of sleep pressure build-up, as expressed in theta-alpha activity during waking EEG. Interestingly, time course

analysis of these data indicated a slower increase in sleep pressure during extended wakefulness in evening than in morning types.

In addition to differences in physiological parameters, the diurnal profile of neurobehavioral variables may also depend on chronotype, as earlier diurnal peaks in alertness and performance have been observed in morning than in evening types (Foret, Benoit, & Royant-Parola, 1982; Kerkhof, 1991; Natale & Cicogna, 1996, 2002). Several studies have examined the temporal fluctuations of performance over the normal working day while considering the individual's circadian preference. In these protocols, performance tests are administered at optimal or non-optimal times of day, as inferred for each subject based on the score obtained on morningness-eveningness questionnaires (Horne & Östberg, 1976). Accordingly, performance peaks have been observed at different clock times depending on an individual's specific chronotype (e.g. Bodenhausen, 1990; Hasher, Chung, May, & Foong, 2002; Hasher, et al., 2005; Hasher, Zacks, & Rahhal, 1999; Horne, Brass, & Pettitt, 1980; Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1998, 1999; Matchock & Toby Mordkoff, 2008; May, 1999; May & Hasher, 1998; May, Hasher, & Foong, 2005; May, Hasher, & Stoltzfus, 1993; Petros, 1990; West, Murphy, Armilio, Craik, & Stuss, 2002). The results suggest that time of day and chronotype matters for cognitive tasks assessing the ability to cognitively control and guide attentional resources and behavior (mainly inhibitory tasks such as stop-signal and go/no-go tasks), but not for tasks that require more automatic processes such as vocabulary tests, simple trivial questions and familiar category judgments (Yang, Hasher, & Wilson, 2007; Yoon, 1997). May and Hasher (1998) proposed that alterations in cognitive functioning at off-peak times actually stem from circadian-related deficits in inhibition. From this perspective, performance at non-optimal times of day would reflect deficits such as increased access to irrelevant information or failure to suppress information that is no longer useful. However, in these studies, morning and evening chronotypes were always tested at the same clock time. Results under those conditions are likely to be explained by confounding factors such as differential circadian phase positions during testing time, differential sleep pressure conditions or carry-over effects of sleep inertia. Accordingly, we recently observed that chronotype-dependent time-of-day modulations are weakened when testing time is adapted to the specific individual's sleep-wake schedule, suggesting that the classically observed synchrony effect may be partially mediated by differences in socio-professional timing constraints, the amount of accumulated sleep need, or circadian phase, all leading to differential arousal levels at testing (Schmidt, Peigneux, Cajochen, & Collette, 2012). Likewise, Mongrain, Noujaim, Blais, & Dumont (2008) mostly observed similarities in diurnal variations in vigilance in the two chronotypes when studied with their preferred sleep schedule.

Humans can also differ in other sleep-wake characteristics, such as sleep length. Even though this phenotypic trait has been less extensively examined, it is

noteworthy that short and long sleepers differ in circadian and homeostatic regulation patterns (Aeschbach, Cajochen, Landolt, & Borbely, 1996; Aeschbach et al., 2001; Aeschbach et al., 2003). It has been suggested that the circadian pacemaker programs a longer biological night in long sleepers than in short sleepers (Aeschbach, et al., 2003). It was also observed that short sleepers present a higher sleep debt, but at the same time are able to better cope with increased homeostatic sleep pressure as compared to long sleepers (Aeschbach, et al., 2001). Overall, the kinetics in homeostatic sleep pressure build-up and dissipation does not seem to differ majorly between long and short sleepers, and some authors suggest that if one offers short sleepers enough sleep opportunities, they might become long sleepers (Klerman & Dijk, 2005).

Genotype-dependent modulations in human sleep and wakefulness

Several genes have been linked to inter-individual differences or even pathologies in human sleep-wake behaviors (for an overview see Landolt, 2008a; Wulff, Porcheret, Cussans, & Foster, 2009). The contribution of genetic factors to individual differences in human sleep traits has been well established, e.g. in terms of diurnal preference (Koskenvuo, Hublin, Partinen, Heikkila, & Kaprio, 2007), EEG patterns during wakefulness, NREM and REM sleep as well as sleep structure and duration (reviewed in Landolt, 2011). The high heritability is not only mirrored in higher similarities of monozygotic compared to dizygotic twins or unrelated persons, but also in high correlations within individuals over time and across different conditions, as well as noticeable variability between individuals (Tan, Campbell, & Feinberg, 2001; Tucker, Dinges, & Van Dongen, 2007; van Beijsterveldt & van Baal, 2002).

A number of genes involved in the generation of circadian rhythmicity have been discovered, among them *CLOCK*, *BMAL1*, genes of the *PERIOD* (*PER*) family and *CRYPTOCHROME* (*CRY*) (Dijk & Archer, 2010). These genes are involved in a complex molecular feedback loop setting the period of the circadian oscillator (see Takahashi, Hong, Ko, & McDearmon, 2008 for a review). Genetic variations in these clock genes have been related to different sleep and circadian phenotypes (Dijk & Archer, 2010). Variants of the human *CLOCK* gene have for example been associated with diurnal preference (Katzenberg et al., 1998; see von Schantz & Archer, 2003 for a review of other studies), and sleep duration (Allebrandt et al., 2010), as well as to be a modulator of differential sleep disturbance patterns in mood disorders (e.g. Serretti et al., 2003). Importantly, a non-circadian role for clock genes in sleep homeostasis has been evidenced (Franken, Chollet, & Tafti, 2001; Franken, Thomason, Heller, & O'Hara, 2007; Laposky et al., 2005; Naylor et al., 2000; Viola, et al., 2007; Wisor et al., 2002; Wisor et al., 2008). These studies found that the expression of a number of clock genes at the cortical level is affected by the sleep-wake history and that the homeostatic sleep regulation is altered in mice that are mutant for one

or more clock genes. Intriguingly, circadian clock genes can also act on homeostatic markers in humans (e.g. Viola, et al., 2007).

Besides, polymorphisms in genes coding for factors potentially involved in the sleep homeostatic process, such as adenosine deaminase (ADA), adenosine receptor A2A (ADORA2A) or brain derived neurotrophic factor (BDNF) were shown to be involved in human sleep-wake regulation and its impact on cognition (Landolt, 2011). In this section, we will focus on the most striking evidence of genetic modulations predicting inter-individual differences in the human sleep-wake behavior and related cognitive performance outputs.

A primate-specific (Jenkins, Archer, & von Schantz, 2005) variable number tandem repeat (VNTR) polymorphism within the clock gene *PERIOD3* (*PER3*) contains a 54-nucleotide unit, which in human, is repeated 4 ($PER3^4$ allele) or 5 ($PER3^5$ allele) times (Archer et al., 2003; Ebisawa et al., 2001). This polymorphism has been shown to influence several variables related to sleep and wakefulness. So far, a number of studies found associations between homozygous carriers of the longer 5-repeat allele ($PER3^{5/5}$) with morning preference (Archer, et al., 2003; Ellis, von Schantz, Jones, & Archer, 2009; Lazar et al., 2012), whereas the shorter 4-repeat allele ($PER3^{4/4}$) was associated with delayed sleep phase disorder (DSPD) (Archer et al., 2003). To add, the association of *PER3* mRNA expression with sleep timing was more robust in $PER3^{5/5}$ than in $PER3^{4/4}$ individuals, suggesting a more rigid circadian control in the former (Archer, Viola, Kyriakopoulou, von Schantz, & Dijk, 2008; Dijk & Archer, 2010). In a prospective study, where young healthy participants were selected solely based on their genotype, $PER3^{5/5}$ carriers showed shorter sleep latencies, an enhancement of SWS and SWA in NREM sleep, as well as a steeper SWA decrease during sleep episodes compared to $PER3^{4/4}$ individuals. Furthermore, greater theta and alpha activity was found during wakefulness in $PER3^{5/5}$ carriers when sleep deprived (Viola et al., 2007). As a response to extended wakefulness, cognitive performance deteriorated faster in homozygous long allele carriers, specifically during late night and early morning hours (Viola et al., 2007). Higher vulnerability of the long allele carriers seems to be especially pronounced for cognitive tasks challenging executive functioning (Groeger et al., 2008). On the other hand, a study investigating chronic partial sleep deprivation (4h/night over 5 consecutive days) following two nights of sleep extension revealed no differences in cognitive performance between genotypes, although differences in a marker of sleep homeostasis (more SWA in $PER3^{5/5}$ carriers) were detected after sleep restriction (Goel, et al., 2009). A recent study exploring the effect of partial sleep restriction (6h/night) as well as acute total sleep deprivation showed that subjective alertness was most impaired in $PER3^{5/5}$ carriers during sleep restriction days compared to the other genotypes (Lo et al., 2012). Likewise, acute total 40h-sleep deprivation implemented after the partial sleep restriction days impacted most on working memory performance of $PER3^{5/5}$ carriers (Lo et al., 2012). Seemingly, the differences in sleep homeostatic parameters between the long and

short allele carriers are stably replicated, while the findings concerning the differences in cognitive performance are discussed controversially. Different study designs, methodology, cognitive task challenge and small group sizes may partially account for this lack of consistency.

The Catechol-O-Methyltransferase (COMT) Val158Met polymorphism, modulating cortical dopaminergic neurotransmission, has been associated with narcolepsy and is suggested to be a predictive factor for individual differences in prefrontal functioning (see Barnett, Scoriels, & Munafo, 2008 for an overview). Regarding sleep and wakefulness, this polymorphism is associated with a modulation in brain alpha oscillations under baseline as well as sleep deprivation conditions (Bodenmann, Rusterholz, et al., 2009). Intriguingly, the stimulant Modafinil, commonly used to treat sleepiness in narcolepsy, maintained baseline performance in sustained attention and executive functioning in Val/Val carriers, but not in Met/Met carriers (Bodenmann, Xu, et al., 2009). In a recent study, Goel and colleagues (Goel et al., 2011) could show that this polymorphism modulates the sleep physiological response to chronic sleep restriction, while neurobehavioral performance variation was similar between Val/Val and Val/Met carriers.

Adenosinergic mechanisms have been suggested to play a key role in sleep homeostasis (Landolt, 2008b). There is evidence from animal studies that the state of prolonged wakefulness is associated with rising levels of adenosine in the basal forebrain, while this protein seems to decline during sleep (Porkka-Heiskanen et al., 1997). An increased extracellular concentration of adenosine achieved by the pharmacological inhibition of its metabolization has been shown to prolong NREM sleep duration (Okada et al., 2003). Interestingly, the activity of one enzyme degrading adenosine irreversibly, adenosine deaminase (ADA), shows systematic stable inter-individual differences in humans, which can be traced back to a single nucleotide polymorphism (SNP) in the coding region of the *ADA* gene. Heterozygous G/A allele carriers, associated with a lower enzymatic activity, report fewer awakenings, show longer deep sleep duration as well as enhanced SWA under normal and high sleep pressure conditions (Bachmann, Klaus, et al., 2012; Battistuzzi, Iudicone, Santolamazza, & Petrucci, 1981; Mazzotti, et al., 2012; Retey, et al., 2005; Riksen et al., 2008). Importantly, genotype-dependent variations were also evident in subjective sleepiness and objective vigilance during total sleep deprivation (Bachmann, Klaus, et al., 2012). The central nervous adenosinergic effects on sleep and sleep EEG are mainly mediated via two subtypes of receptors, the A1 and A2A (ADORA2A) receptors (Landolt, 2008b). In the coding region of the *ADORA2A* gene a SNP has been associated with variations in sleep-wake regulatory processes. Its significance has been related to its linkage with a polymorphism in the 3'UTR of *ADRORA2A* potentially implicated in the modulation of differences of the A2A receptor expression levels (Alsene, Deckert, Sand, & de Wit, 2003). Compared to carriers of the C allele, homozygous T allele carriers have a reduced EEG power in the 7-

10 Hz range during sleep and waking, perform better in a vigilance task after sleep restriction and show less power in the beta range in recovery sleep following sleep deprivation during which caffeine was administered (Retey et al., 2005; Retey et al., 2007; Rupp, Wesensten, Newman, & Balkin, 2012). These differences between the genotypes may be attributed to differences in receptor-mediated signal transduction and receptor sensitivity (Landolt, 2011; Rupp, Wesensten, & Balkin, 2012). Recently, Bodenmann and colleagues (Bodenmann et al., 2012) identified a haplotype regarding the combination of eight distinct SNPs of the A2A receptor gene predicting differences in sustained attention existing irrespectively of the sleep pressure level. However, the specific neuroanatomical and neuropharmacological aspects varying with every single SNP, as well as the nature of their interaction remain to be elucidated.

A large body of research supports a crucial role of sleep regarding synaptic plasticity, learning and memory consolidation (Diekelmann & Born, 2010; Maquet, 2001; Tononi & Cirelli, 2006). In the animal model, one factor representing a potential causal link between sleep homeostasis as indicated by the SWA level and cognitive waking performance on the other hand is the brain derived neurotrophic factor (BDNF) (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008; Huber, Tononi, & Cirelli, 2007). In humans, a SNP on the *BDNF* gene is associated with variations in its activity-dependent secretion and related to differences in cognitive performance (Dempster et al., 2005; Egan et al., 2003; Goldberg et al., 2008; Hariri et al., 2003; but no differences in van Wingen et al., 2010 – reviewed in Bekinschtein, Cammarota, Izquierdo, & Medina, 2008). Bachmann and colleagues (Bachmann, Klein, et al., 2012) found that this genotype does not only affect working memory performance during conditions of rising and high sleep pressure, but also seems to contribute to deep sleep stage 4 duration as well as the level of SWA at the beginning of baseline sleep and a recovery night after sleep deprivation. In perspective of a strong heritability of brain architectural aspects and reported associations between this specific SNP and neuroanatomical phenotypes, it is important to note that the functionality of the SNP regarding circulating BDNF levels in humans is still unknown (Bachmann, Klein, et al., 2012). Thus, it cannot be ruled out that differences in SWA stem from systematic variations in brain anatomy related to this BDNF polymorphism.

Impact of the sleep-wake cycle on cognition-related cerebral activity

Trait-like differences in response to sleep loss have also been shown in the cerebral activity underlying cognitive effort (Chee & Chuah, 2008; Figure 3). Functional brain imaging studies have reported correlations between brain

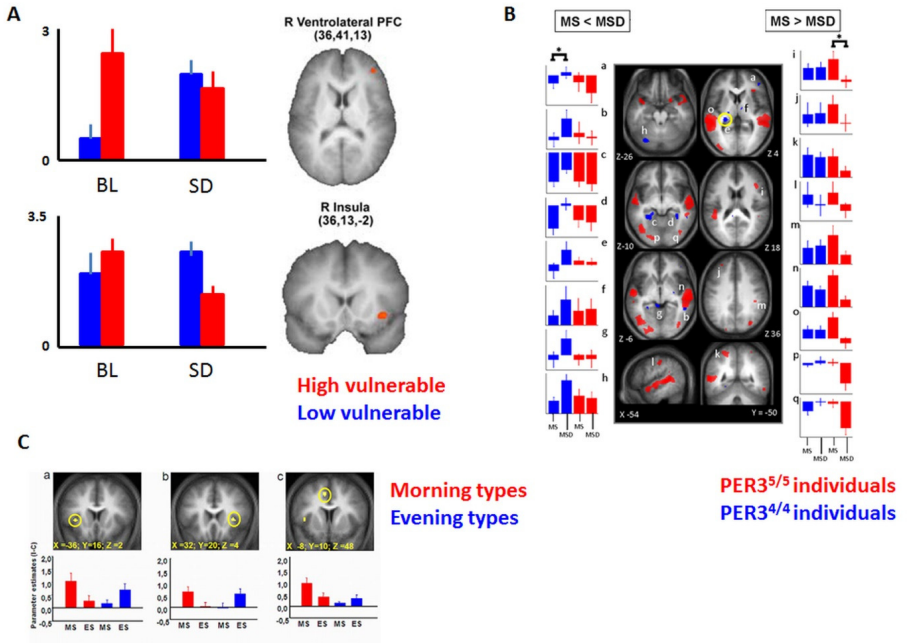

Figure 3. Evidence of activation increase from well rested to sleep deprivation conditions in individuals less vulnerable to sleep deprivation and activation decrease in more vulnerable participants (A&B). A similar pattern can be observed from the morning to the evening hours for chronotypes, also supposed to differ in their vulnerability to increasing homeostatic sleep pressure (C).
(A) Top panel: parameter estimates of cognitive inhibition-related activation in the right ventrolateral prefrontal cortex are plotted as a function of state (BL, rested baseline; SD, sleep deprivation) and group (low vulnerability in blue versus high vulnerability in red). A significant interaction of state by group indicates that individuals who best maintain inhibitory efficiency after sleep deprivation have lowest activation at rested wakefulness, whereas those most vulnerable to sleep loss show the highest activation. After sleep deprivation, this pattern is reversed. Lower panel: average activation parameter estimates in the right insula plotted as a function of state and group. Activation increased for individuals least vulnerable to sleep deprivation, whereas activation decreased in the other group (adapted from Chuah, Venkatraman, Dinges, & Chee, 2006).
(B) Significant differences in brain responses between fMRI sessions recorded after 25 h (MSD; morning after sleep deprivation) and 1.5 h (MS; morning after sleep) of wakefulness. Left panel: significantly increased activation from MS to MSD in *PER3*$^{4/4}$ individuals (blue). Right panel: significant activity decreases from MS to MSD in *PER3*$^{5/5}$ participants (red; reprinted with permission from Vandewalle, Archer, et al., 2009).
(C) Interference-related responses according to time of day (MS: morning session; ES: evening session) and chronotype (red: morning types; blue: evening types). Displays show areas (highlighted in yellow) in which activity is associated with a task-related interaction effect between Chronotype and Session. Corresponding parameter estimates are displayed. Similar BOLD activation profiles were also observed for more posterior cortical areas (reprinted with permission from Schmidt, Peigneux, Leclercq, et al., 2012).

activation and performance declines after sleep deprivation. For example, individual differences in the vulnerability to fatigue after sleep deprivation are related to baseline differences in cortical, mainly frontal, activations during the performance of a working memory task (Caldwell et al., 2005). Others (Mu et al., 2005) examined whether differences in patterns of brain activation under well-rested conditions relate to the differences in vulnerability to sleep deprivation as manifested in performance of a working memory paradigm. They revealed that task-related activity decreased for all subjects following sleep deprivation, but resilient subjects were characterized by higher task-related baseline activity during rested wakefulness than vulnerable individuals. Inter-individual variability in response to sleep deprivation has also been revealed for a cognitive interference paradigm (Chuah, Venkatraman, Dinges, & Chee, 2006). Individuals who are better able to maintain inhibitory efficiency after sleep deprivation could be distinguished by lower task-related, phasic activation of the right ventral prefrontal cortex during rested wakefulness (Figure 3). These persons also showed a greater activation rise (interpreted as greater cognitive capacity) in this prefrontal area as well as in the right insula after sleep deprivation relative to those participants whose inhibitory efficiency declined. It appears thus to be important to take into account these inter-individual differences in response to sleep loss when assessing the effects of sleep deprivation on cognition and its cerebral correlates (Chee & Chuah, 2008).

Interestingly, a recent study revealed that the above-described polymorphism in the human clock gene *PER3* might partially account for differential vulnerability to sleep loss at the cerebral level (Vandewalle, Archer, et al., 2009; see also Figure 3). The authors acquired functional magnetic resonance imaging (fMRI) data during the performance of a working memory task after a night of normal sleep and after sleep deprivation. Subjects were selected on basis of their *PER3* polymorphism, being either homozygous for the long or the short repeat allele (see section 4). It was observed that blood oxygen level dependent (BOLD) activity modulations of brain responses to a working memory task over the 24-hour cycle followed the dynamics predicted by the interplay between circadian and homeostatic processes according to each subject's specific genotype. When comparing both morning sessions, after 1.5 h or 25 h of wakefulness, $PER3^{5/5}$ subjects showed widespread decreased cortical activations after 25 hours of wakefulness, while the more resistant $PER3^{4/4}$ individuals did not present any decreased task-related brain responses, but rather recruited supplemental cortical regions in response to a sleep homeostatic challenge (see also Vandewalle & Schmidt, 2013).

It is worth noting here that BOLD responses underlying working memory performance of the vulnerable $PER3^{5/5}$ and more resistant $PER^{4/4}$ individuals already revealed differential activation profiles over a normal 16 hours waking day. From the morning to the evening, $PER3^{4/4}$ individuals did not show any significant changes in brain responses to the task, while $PER3^{5/5}$ individuals

presented decreased activation in an area of the posterior dorsolateral prefrontal cortex.

First evidence suggesting that the brain state changes during a normal day to maintain wakefulness comes from a positron emission tomography (PET) study (Buysse et al., 2004). Compared to the morning, evening rested wakefulness was associated with increased hypothalamic and brainstem metabolism, putatively implicated in arousal promotion. Decreased metabolism was also detected in temporal and occipital cortices. A number of recent fMRI studies also explored time of day modulations underlying cognitive performance at different times of the day. One study analyzed diurnal BOLD activity variation involved in orienting attention and executive control processes by performing a modified version of the Stroop Color-Word task in the fMRI environment at five different times of the day (Marek et al., 2010). A significant time-of-day-dependent BOLD activity modulation was found in brain regions related to the orienting attentional system, such as the parietal lobe and frontal eye fields. Moreover, activations in areas of the executive control system were found. For most of these regions an activation decrease was observed from the morning (6am) to the evening (6pm) hours, except for the last time point (around 10 pm), were a relative activity increase was observed again.

Other studies showed that the chronotype has the potential to significantly affect time-of-day-dependent modulation patterns in the cerebral correlates underlying cognitive task performance. A recent fMRI study investigated the cerebral correlates underlying a self-paced finger-tapping task at different times of the day (morning, midday, afternoon, and evening) and according to chronotype (Peres et al., 2011). The BOLD signal showed systematic differences across the day in task-related motor areas of the brain. Furthermore, these daily modulations were associated with morningness-eveningness such that the later the chronotype, the later the time-of-day when participants reached maximal task-related neural activity. In an earlier study, we similarly investigated the impact of chronotype and time of day on fMRI derived BOLD activity (Schmidt, et al., 2009; Schmidt, Peigneux, Leclercq, et al., 2012). We aimed at characterizing our study population with respect to the timing of their circadian rhythmicity (by estimating circadian phases through collection of salivary melatonin) and to their accumulated homeostatic sleep pressure, by assessing the amount and time course of sleep SWA in the night preceding the fMRI sessions. Such a characterization might be of crucial interest considering that chronotypes differ in the dynamics of sleep-wake regulation processes (see section 4). In congruence with the literature, we observed that morning type individuals are more vulnerable to the accumulation of time spent awake than evening types during the subjective evening hours. They presented increased levels of sleep SWA at the beginning of the night, paralleled by behavioral differences between chronotypes, with morning types expressing higher subjective sleepiness and lower objective vigilance levels in the evening hours as compared to evening types. Importantly,

at this time of the day, the putative circadian arousal signal tends to counteract the increase in homeostatic sleep pressure associated with sustained wakefulness. Thus, it may be assumed that the circadian signal is acting less efficiently in morning as compared to evening types, either due to or leading to the disproportionally increased homeostatic sleep pressure in morning types. Functional neuroimaging data acquired during task performance at different times of the day may provide insights to probe these assumptions. We first investigated sustained attention considered as "a fundamental form of attention on which many other cognitive processes build" (Raz & Buhle, 2006). Maintenance of optimal attentional performance in the subjective evening hours was associated with higher activity in evening than morning chronotypes in a region of the locus coeruleus (LC) and in an anterior hypothalamic region putatively encompassing the suprachiasmatic area (SCA; Schmidt, et al., 2009). Importantly, both regions represent key areas involved in the generation of the circadian arousal signal (Aston-Jones, Chen, Zhu, & Oshinsky, 2001). We further observed that activity in the SCA decreased with increasing homeostatic sleep pressure as assessed by SWA in the first sleep cycle, suggesting an influence of homeostatic and circadian interactions on the neural activity underlying time-of-day variations in human cognition. In a next step, we explored whether these patterns of regional cerebral activity underlying homeostatic and circadian sleep regulatory differences between morning and evening types are generalizable across different cognitive domains. There is evidence that circadian phase, time spent awake and sleep regulate neurobehavioral performance in a task-specific manner. We chose to investigate morning-evening variations in cognitive interference over conflicting information using a classical Stroop paradigm (Schmidt, Peigneux, Leclercq, et al., 2012). Our results yield evidence that morning types exhibit decreased task-related BOLD responses in brain areas involved in conflict resolution (e.g. insula, cingulate cortex) from the morning to the evening hours, whereas evening chronotypes show the reverse pattern (Figure 3). Further regression analyses revealed that Stroop-related activity in the postero-lateral hypothalamus during evening hours is associated with homeostatic sleep pressure in a chronotype-specific manner, such that a negative relation between sleep SWA at the beginning of the night and task-related BOLD activity in this hypothalamic region was observed in morning types only. With respect to the latter result, it is hypothesized that decreased task-related BOLD activity in morning types during the evening is due to a relative disruption in the transmission of the alerting signal generated by hypothalamic areas into cortical areas involved in the successful performance of the ongoing task (Schmidt, Peigneux, Leclercq, et al., 2012).

Note that results of these studies were acquired under normally entrained day-night conditions. As described above, circadian and homeostatic processes always vary together during a normal waking day. A criticism that might be addressed to these studies is their inability to more precisely level out circadian

and homeostatically driven contributions, as well as their interactive effects on the investigated variables.

It would be intriguing to use the previously described FD, CR or ultra-short sleep-wake cycle protocols to track the homeostatic and circadian influences on the cerebral bases underlying arousal and higher-order cognitive behaviors. As compared to previous fMRI studies, such a program would allow one to continuously investigate the interaction of these influences at different times by repetitive task administration over the 24-hour cycle.

Clinical considerations: Light therapy

A lot of translational research has been performed in the field of human sleep and chronobiology research (Wirz-Justice, 2010) and a multitude of simple therapeutic tools have been derived. Consolidated periods of sleep and wakefulness at appropriate times throughout the 24-hour cycle are supportive for well-being, cognitive performance and the health status in general.

The physiological functions and implications of daily sleep–wake rhythms on our health are being intensely explored nowadays and become more and more important, considering that people are increasingly forced to be awake at inappropriate or at biologically non-optimal times during shift work (Cajochen, Chellappa, & Schmidt, 2010). Associations between shift work and physical health have been widely addressed (Vogel, Braungardt, Meyer, & Schneider, 2012) and a possible relationship between the demands of the modern working society, affecting our sleep-wake behaviour, and increases in psychiatric and psychosomatic diseases has been suggested (Vogel, et al., 2012). Concomitantly, sleep and circadian rhythm disruption are frequently encountered in psychiatric disorders (see Wulff, Gatti, Wettstein, & Foster, 2010 for a review).

Agents that have the potential to affect the circadian system have been assessed for their efficiency in clinical settings, one of them being light. Light represents the main zeitgeber of the circadian system and allows appropriate entrainment to the external light-dark cycle. To achieve photoreception and entrainment of circadian rhythms by light, specialized photoreceptors in the mammalian eye communicate information about environmental light to the circadian clock located in the SCN via a neuroanatomical pathway called the retino-hypothalamic tract (Duffy & Wright, 2005). Those pathways do not rely exclusively on rods and cones; a third type of photoreceptor cell is involved, which is localized in the ganglion cell layer of the retina (Berson, Dunn, & Takao, 2002; Hattar, Liao, Takao, Berson, & Yau, 2002) containing melanopsin as the relevant photopigment (Fu et al., 2005; Hattar, et al., 2002).

Non-visual acute effects of light have been hypothesized to be stronger when light contains a greater portion of blue light (Cajochen, 2007; Münch & Bromundt, 2012). In this perspective, fMRI studies revealed an extensive involvement of light in the regulation of human brain functions, acting in both a brain-region-specific and a wavelength-specific manner (Vandewalle, Maquet, &

Dijk, 2009). Especially monochromatic blue light was able to modulate activity in subcortical structures involved in alertness and dynamically promoted cortical activity in cognitive networks (Vandewalle et al., 2006; Vandewalle, Gais, et al., 2007; Vandewalle, Maquet, et al., 2009; Vandewalle, Schmidt, et al., 2007). Intriguingly, even light emitting diode (LED) computer screens, containing more blue light, had stronger effects on subjective alertness and cognitive performance than conventional screens (Cajochen et al., 2011). Inter-individual differences have also been evidenced in the responsiveness to acute effects of light. In a recent study, we observed for instance that individuals with a specific genotype of *PER3* (*PER3*$^{5/5}$) show a greater sensitivity to the alerting effects of blue-enriched light as compared to carriers of another genetic variant (*PER3*$^{4/4}$*;* Chellappa et al., 2012).

Timed bright light exposure can be used as a countermeasure for sleepiness and fatigue during night work or for resynchronization to the external light-dark cycle after daytime shifts or jet lag (Münch & Bromundt, 2012). The consequences of circadian misalignment due to shift work encompass disturbed sleep and general health risks, but also decreased alertness and cognitive deficits, potentially leading to safety and health threatening mistakes (Burgess, Sharkey, & Eastman, 2002). Well-administered bright light exposure can be used as a tool to shift the circadian phase accordingly, but can also elicit acute beneficial effects on alertness and cognitive performance during the shifts (e.g. Boivin, Boudreau, & Tremblay, 2012; Burgess et al., 2002; Czeisler et al., 1990; Roth, 2012).

In sleep medicine, circadian-related sleep disorders, such as the delayed or advanced sleep phase syndrome can be specifically treated with light exposure (Wirz-Justice & Bromundt, 2013). The timing of light exposure is of crucial interest here. Generally speaking, the following rule can be applied according to the phase response curve of light (Czeisler et al., 1989; Jewett, Kronauer, & Czeisler, 1991; Jewett et al., 1997): strongest circadian phase delays are observed when light exposure occurs in the evening or early night hours, while maximum advances occur after light exposure in the early morning hours. Sleep restriction is conventionally used to counter too early or too late sleep times (Wirz-Justice, 2010). However, attempts to shift inappropriate timing of sleep are often much more effective when combined with timed light exposure. Importantly, sleep disorders such as delayed sleep phase syndrome can represent prodromal stages in the course of psychiatric diseases (Wirz-Justice & Bromundt, 2013).

The activating and antidepressant effects of light are mostly achieved through indirect effects of a consolidation of the sleep-wake cycle (Wirz-Justice & Bromundt, 2013), although more direct mechanisms have also been highlighted acting on several neurotransmitter systems, especially on serotonergic networks, playing an important role in the regulation for affective states, but also for sleep and wakefulness (Wirz-Justice & Bromundt, 2013). Light therapy is not only considered as the therapy of choice for seasonal affective disorders (SAD; Terman & Terman, 2005), but is also increasingly assessed for the treatment of

non-seasonal forms of depression (Terman & Terman, 2005) or other psychiatric diseases, such as borderline personality disorder (Bromundt et al., 2012), antepartum depression (Wirz-Justice et al., 2011) or bulimia nervosa (Lam, Goldner, Solyom, & Remick, 1994).

Another application example of light therapy can be found in the domain of neurological disorders associated with major disturbances in the rest-activity rhythm, such as Alzheimer's disease (AD). In AD patients, nighttime sleep is fragmented and daytime activity is disrupted by multiple napping episodes (Dowling et al., 2005; Van Someren, Hagebeuk, Lijzenga, Scheltens, de Rooij, Konker. et al., 1996). Encouraging results point into the direction of a beneficial effect of bright light exposure on rest-activity profiles in home dwelling demented residents (e.g. Dowling et al., 2005; Van Someren et al., 1999). Light installations for a long-term daily treatment with whole-day bright light in elderly residents can have an impact on cognitive deterioration evaluated by the Mini-Mental State Examination Scale and has the potential to slightly improve depressive symptoms (Riemersma-van der Lek et al., 2008).

Taken together, a lot of promising light applications as a therapeutic agent have been investigated in different fields. The side effects of light therapy are rare and the therapy costs small, such that its application alone or as an adjuvant therapy in several medical fields may be advised, even though the treatment efficiency in each specific field should first be scientifically proven.

Conclusion

In humans, sex, age, chronotype, habitual sleep duration, but also a series of functional genetic variants have been shown to impact on basic sleep-wake regulatory processes, which act at multiple levels to allow our body to work efficiently on the basis of our planet’s 24-hour light-dark cycle. At a fundamental level, the investigation of any population presenting characteristic differences in the expression of these basic mechanisms may represent a fascinating tool to explore how and why human beings are able to sleep and wake at appropriate times and spend suitable durations in the different vigilance states of adequate quality, according to their internal needs. Addressing these questions at different levels, ranging from basic molecular processes to complex human behaviors and their cerebral correlates, should allow us to discover where these processes converge in generating the diverse sleep-wake patterns we see in human beings. The understanding of these fundamental processes should contribute to the development of novel, as well as to the fine tuning of already existing therapeutic tools, acting on the human sleep-wake behavior on an individually-tailored basis (Rajaraman, Gribok, Wesensten, Balkin, & Reifman, 2008).

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