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CIRCADIAN AND SLEEP-WAKE DEPENDENT IMPACT ON NEUROBEHAVIORAL FUNCTION

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Variations in waking neurobehavioral or cognitive functioning are closely linked to endogenous 24-h rhythm (circadian pacemaker) and time awake. We summarize studies in which the contribution of the circadian pacemaker and time awake on neurobehavioral function was investigated. Stable and high levels of attention and vigilance can only be maintained when the circadian timing system opposes the wake-dependent deterioration of alertness and performance. Planning performance in a maze tracing task was also affected by time awake, whereas circadian modulation was less pronounced. Additional to circadian phase position and the level of sleep pressure, rapid eye movement sleep may play a role in acquiring specific procedural skills in a sequence learning task. We conclude that circadian phase and time awake have a substantial impact on short and stimulating planning tasks, which are related to the prefrontal cortex, and on sequence learning that requires activation of striatal brain regions.

One of the distinguishing characteristics of sleep throughout much of the animal kingdom is that the periods of sleep and wake occur at specific times of the day and/or night. In mammals, the central circadian (i.e., 24 hours) pacemaker that regulates the timing of sleep and wake as all 24-hours rhythms, is located in a small region of the hypothalamus (the suprachiasmatic nuclei [SCN]), whereas the control of sleep and wake *per se* appears to involve many diverse regions of the brain. Waking neurobehavioral function is directly affected by the timing of sleep and wakefulness. In the present review, we emphasize two facets of "time", the effect of "internal biological time" and "time spent within a vigilance state" (i.e., wakefulness, sleep). "Internal time" is driven by the endogenous circadian pacemaker (circadian clock-like process) which requires daily synchronization with "exter-

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nal time" (i.e., time of day). The other dimension, "elapsed time" spent into wakefulness and sleep, reflects a homeostatic hourglass process, which is continuously depleted or replenished depending on the vigilance state. The homeostat reflects the current drive for sleep, which increases with time awake and decreases in a nonlinear fashion during sleep. We summarize the importance of circadian and homeostatic aspects as an integral part of the regulation of waking neurobehavioral function. We also provide evidence that circadian phase, time awake and sleep *per se* play an important role not only in regulating neurobehavioral performance related to sustained attention but also to sequence learning and planning performance.

The Circadian and Homeostatic Process and Their Interaction

Early studies indicated that sleep homeostasis, the sleep-wake dependent regulation of sleep, can not solely account for changes in sleep propensity. In humans, total sleep loss is only compensated by a ~ 20% increase in sleep duration during the following recovery night (Patrick and Gilbert, 1896; in Gulevich, Dement, & Johnson, 1966). This had led to the assumption that, besides the homeostatic process, one or more processes must be involved in the regulation of sleep duration. In fact, it was realized that such variations in sleep duration occur in a consistent and predictable manner which depends on when subjects go to sleep (i.e., time of day; Czeisler, Weitzman, Moore-Ede, Zimmerman, & Knauer, 1980; Strogatz, Kronauer, & Czeisler, 1986; Zulley, Wever, & Aschoff, 1981). The role of "time of day" as the circadian process C and the homeostatic process S have been conceptualized in the two-process model in order to predict sleep propensity in humans (Borbély, 1982; Daan & Beersma, 1984). According to this model the timing of sleep and wakefulness is determined by the interaction of the circadian process C, generated by an endogenous circadian clock, and the homeostatic process S.

Brain structures governing the homeostatic process S are not yet known. In contrast, circadian rhythms are controlled by a specific brain structure, the master circadian pacemaker, located in the SCN of the anterior hypothalamus (for a review see Moore, Speh, & Leak, 2002). Recent progress in molecular biology unraveled canonical clockwork genes, and how these genes encode circadian time such that clock outputs are converted into temporal programs for the whole organism (for a review see Herzog & Schwartz, 2002; Reppert & Weaver, 2002). On a behavioral level, clock outputs can be assessed by measuring overt rhythms such as the circadian rhythm of core body temperature, plasma melatonin, or cortisol concentration etc. These variables, when assessed under appropriate conditions, represent markers of circadian phase, period and amplitude – all parameters of "internal time". The classical mark-

er of the homeostatic process S is slow-wave (SWA) or delta activity during non-REM sleep (Borbély, 1982; Borbély, Baumann, Brandeis, Strauch, & Lehmann 1981; Feinberg, Baker, Leder, & March, 1988). In fact, all model simulations of the two-process model were initially based on SWA during non-REM sleep in humans and animals (Achermann, 1992; Franken, Tobler, & Borbély, 1993).

How the circadian and the homeostatic process interact has not been firmly established. It is not clear at which level this interaction occurs and whether the central circadian oscillator in the SCN directly or indirectly interacts with brain centers responsible for sleep homeostatic processes. Studies with SCN lesioned animals showed that the homeostatic process is still intact and not altered in these animals (Edgar, Dement, & Fuller, 1993; Tobler, Borbély, & Groos, 1983), which indicates that the two processes are, at the brain level, independent from each other. Another possibility is that C and S interact more downstream in the cascade or that the output variables we measure do not reflect a true interaction, but are biased by our metrics (for a discussion see Achermann, 1999; Dijk, 1999). To conclusively show how circadian and homeostatic processes interact with each other, and in order to quantify their strength in the control of sleep and wakefulness, protocols must be applied which allow for separation of the two processes.

Desynchronization of the Circadian and Homeostatic Process

It has been recognized early on that for a better understanding of the mechanisms underlying the timing of the sleep-wake cycle a distinction should be made between internal and environmental factors that both contribute to variations in the propensity to initiate and terminate sleep. Nathaniel Kleitman (1987) was the first investigator to conduct an experiment in which human beings were studied in the absence of periodic cues in the external environment. He realized that in order to prove the existence of internal time or the existence of endogenous self-sustained rhythms, paradigms must be applied that allow for a desynchronization of internal time from external time. In the Mammoth Cave, Kentucky, in 1938, he scheduled subjects to live on artificial day-lengths, which deviated from 24 hours. Under such conditions near 24-h rhythms (circadian) were not able to entrain to the new imposed day length, but continued to oscillate with their endogenous period. It was possible to separate the influence of the timing of the sleep-wake schedule from that of the circadian pacemaker. This imposed desynchrony between the sleep-wake schedule and the output of the circadian pacemaker driving the temperature rhythm occurs only under conditions in which the non-24-h sleep-wake schedule is outside the range of entrain-

ment or range of capture of the circadian system. This protocol has been termed the forced desynchrony protocol. In these protocols scheduled sleep and wake episodes occur at virtually all circadian phases (Figure1).

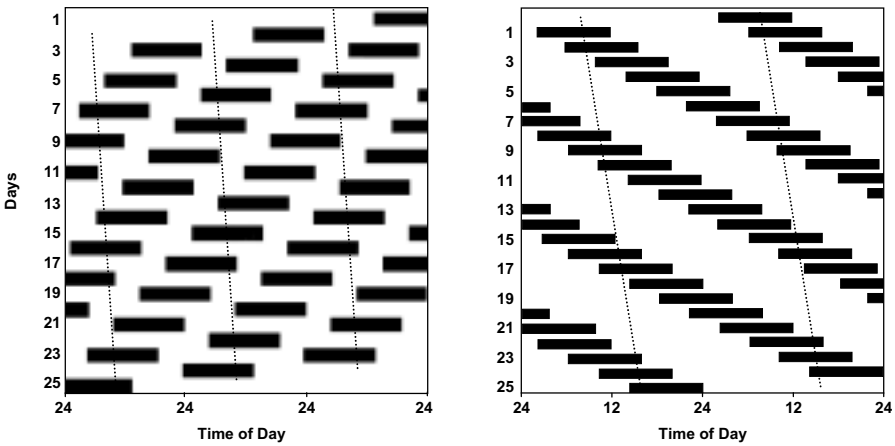

Figure 1. left-hand panel: Triple-raster plot of a 25-day forced desynchrony protocol. Each successive 24-h period is plotted next to and beneath each other. In this example habitual bedtime was at 24:00 h and habitual wake time at 08:00 h. After three baseline cycles of 24 h (not included in the figure), the subjects were placed on a 42.85-h rest-activity cycle and light-dark cycle during which the subjects were scheduled to be awake for 28.57 h (light <15 lux) and asleep for 14.28 h (light <0.03 lux). The black bars indicate the distribution of scheduled sleep episodes throughout the protocol. Dashed lines indicate the fitted maximum of the endogenous circadian melatonin rhythm across days, which drifted to a later phase position relative to clock time. In this example the intrinsic circadian period of the melatonin rhythm was assumed to be 24.2 h. The data are plotted with respect to clock time. Right-hand panel: Triple-raster plot of a 25-day forced desynchrony protocol. In this example the subjects were placed on a 28-h rest-activity cycle and light-dark cycle during which the subjects were scheduled to be awake for 18.7 h and asleep for 9.3 h.

When light intensities during scheduled waking episodes are kept low, the pacemaker free runs with a stable period in the range of 23.9 - 24.5 hours (Czeisler et al., 1999). Furthermore, since subjects are scheduled to stay in bed in darkness, the variation in the amount of wakefulness preceding each sleep episode is minimized. It is thus possible to average data either over successive circadian cycles or over successive sleep or wake episodes and to thereby separate these two components. This averaging serves to isolate the circadian profile of the variable of interest by removing the contribution of the confounding sleep-wake dependent contribution or vice versa in the averaging process (i.e., subtracting background noise which is not temporally related to the evoked component). The efficacy of the forced desynchrony protocol in removing or uniformly distributing several driving factors is

demonstrated by the observation that the observed period of the pacemaker was nearly identical in forced desynchrony protocols with markedly different cycle lengths (for example: 11, 20, 28, or 42.85 hours) and with markedly different levels of physical activity (Czeisler et al., 1999; Hiddinga, Beersma, & Van Den Hoofdakker, 1997; Wyatt, Ritz-De Cecco, Czeisler, & Dijk, 1999). So far, forced desynchrony protocols were applied to quantify circadian and sleep homeostatic changes in sleep, sleep structure, and EEG power density during non-REM and REM sleep as well as during wakefulness (for a review see Cajochen & Dijk, 2003). More recently, also quantitative aspects of circadian and homeostatic regulation of neurobehavioral function during forced desynchrony have been reported (Wright Jr, Hull & Czeisler, 2002; Wyatt et al., 1997, 1999).

Interaction of the Circadian System and the Sleep Homeostat on Neurobehavioral Function

Sleep deprivation alone results in a reduction of neurobehavioral performance. In addition, circadian rhythmicity has been demonstrated in a number of neurobehavioural variables, including: vigilance, arithmetic, serial search, choice reaction time, and short term memory (for a review see Rogers, Dorrian, & Dinges, 2003). There is an endogenous daily rhythm (i.e., circadian) of each of these variables that reaches a minimum just after the minimum of the endogenous component of the temperature rhythm. The homeostatic and the circadian process develop independently, but their interaction determines the timing, duration, and quality of both sleep and wakefulness and also neurobehavioral function. Besides the forced desynchrony protocol, so called constant routine protocols (CR) have been designed and applied to reveal unmasked circadian rhythms (Czeisler, Brown, Ronda, & Kronauer, 1985; Mills, Minors, & Waterhouse, 1978). In the CR protocol, participants are subjected to a regime of more than 24 hours of wakefulness in dim light. Subjects stay in a semi-recumbent position. Hourly iso-caloric snacks provide a constant energy supply. The advantage of a CR protocol is that masking such as posture changes, light level, food intake, physical activity etc. are highly controlled and therefore allow assessment of physiological circadian rhythms which are considered to reflect unmasked circadian pacemaker activity measured under these constant conditions. However, in contrast to a forced desynchrony protocol, there is no desynchronization between the sleep–wake cycle and the circadian pacemaker – which does consequently not allow for a separation of these two processes. Therefore, the effects of prolonged wakefulness (> 24 hours) in a CR protocol are superimposed on the circadian profile of various neurobehavioral variables

(Cajochen, Khalsa, Wyatt, Czeisler, & Dijk, 1999; Cajochen, Knoblauch, Kräuchi, Renz, & Wirz-Justice, 2001; Carrier & Monk, 2000; Dijk, Duffy, & Czeisler, 1992; Doran, Van Dongen, & Dinges, 2001; Johnson et al., 1992; Van Dongen & Dinges, 2000).

Recently, the contribution of the circadian pacemaker and the sleep homeostat to sleep duration and consolidation and to subjective alertness and cognitive performance has been quantified in a forced desynchrony protocol (Wyatt et al., 1999) (Figure 2). This protocol revealed that even within the range of 0 to 18 hours of wakefulness, the contribution of the sleep homeostat to variations of alertness, performance and sleep propensity was equal to the contribution of the circadian pacemaker. The data further revealed that the detrimental effects of prior wakefulness on alertness were strongest close to the minimum of the endogenous core body temperature rhythm. The interpretation of these

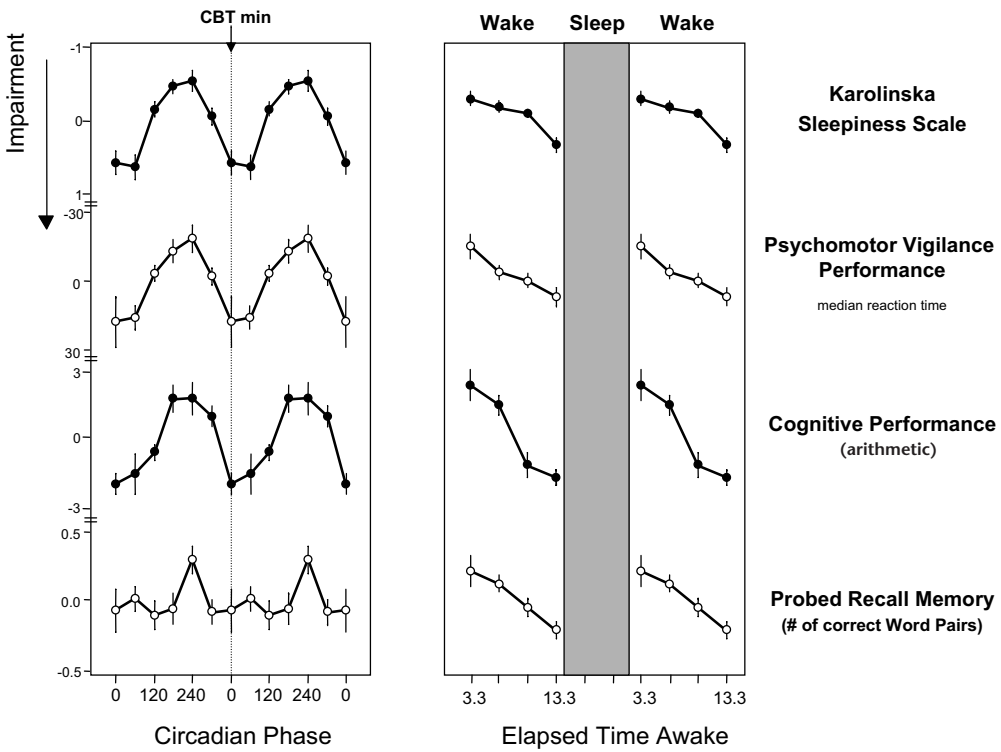

Figure 2. Double plots of main effects of circadian phase relative to minimum of core body temperature (left) and duration of prior scheduled wakefulness (right) on neurobehavioral measures. Plotted points show deviation from mean values during forced desynchrony section of protocol and their respective SEMs. For all panels, values plotted lower in panel represent impairment on that neurobehavioral measure. According to Wyatt et al. (1999).

data led to the conclusion that stable and high levels of alertness can only be maintained when the phase relationship between the endogenous circadian timing system and the sleep/wake cycle is such that the circadian timing system opposes the wake-dependent deterioration of alertness and performance as conceptualized in the "opponent process" model (Dijk & Czeisler, 1994; Dijk et al., 1992; Johnson et al., 1992; Klein et al., 1993) (Figure 3).

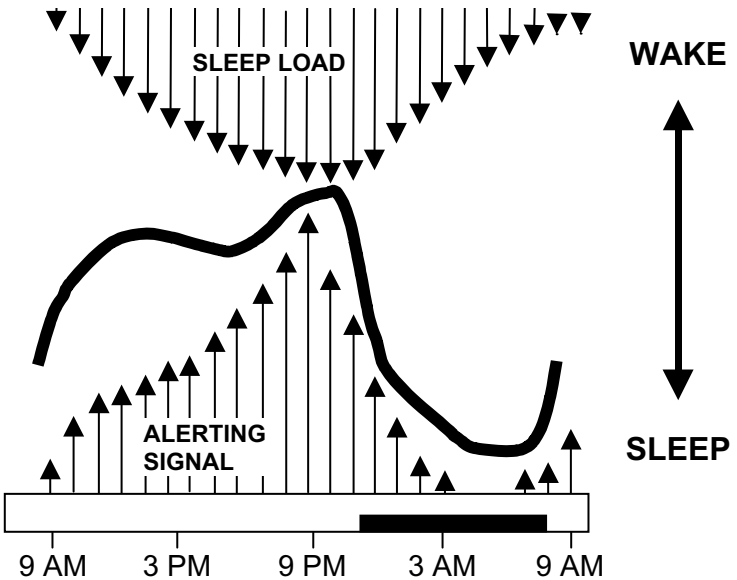

Figure 3: Schematic of the "opponent processes" mediating physiological sleepiness as a function of time of day. Sleep load increases in response to wakefulness imposed and/or maintained by the pacemaker in the SCN. Increasing levels of SCN-dependent alerting over the subjective day opposes homeostatic sleep drive, both of which peak shortly before the habitual sleep phase. According to Edgar et al. (1993).

This is achieved most effectively when the waking day is initiated approximately 2 hours after the endogenous circadian minimum of the core body temperature rhythm, which corresponds to approximately 3 hours after the circadian maximum of the plasma melatonin rhythm. This implies that even modest changes in the phase relationship between the endogenous circadian timing system and the sleep/wake cycle will result in a deterioration of alertness and performance during the waking day. Such effects of moderate sleep loss can become especially pronounced at specific circadian phases, such as the mid-afternoon. It is at this phase that the circadian drive for wakefulness is not sufficiently strong to counteract the increased sleep pressure related to moderate sleep loss.

Recent studies looking at the effects of cumulative sleep loss during restricted sleep schedules (i.e. 4-6 hours sleep per day), reported cumulative increases in subjective and objective sleepiness (Brunner, Dijk, & Borbély, 1993; Carskadon & Dement, 1981; Dinges et al., 1997) and decrements in vigilance performance (Brunner et al., 1993; Dinges et al., 1997). Chronic restriction of sleep to 6 h or less per night produced cognitive performance deficits equivalent to up to 2 nights of total sleep deprivation (Van Dongen, Maislin, Mullington, & Dinges, 2003). These findings corroborate the fact that even relatively moderate sleep restriction can seriously impair waking neurobehavioral functions in healthy adults. Interestingly, sleepiness ratings suggested that subjects were largely unaware of these increasing cognitive deficits, which may explain why the impact of chronic sleep restriction on waking cognitive functions is often assumed to be benign. Remarkably, the changes in cognitive performance functions over days of sleep restriction were not matched by progressive changes in sleep architecture over days. Therefore, it appears that the concept of homeostatic sleep drive cannot solely account for the cumulative neurobehavioral performance changes observed across consecutive days of sleep restriction in this study. This suggests that sleep debt is perhaps best understood as resulting in additional wakefulness that has a neurobiological "cost" which accumulates over time (Van Dongen et al., 2003). It may be that the temporal regulation of sleep and wakefulness regulated by the interplay of circadian and homeostatic processes serves to protect human neurobehavioral functions from degradation due to excessive wakefulness within and between circadian cycles.

Possible Mechanisms Underlying Neurobehavioral Performance Deficits Related to Sleep Loss and Circadian Phase

One important area of the brain that is fundamental to neurobehavioral functioning is the prefrontal cortex (PFC). A number of performance tasks thought to be putatively subserved by the PFC have been reported to demonstrate significant impairment during sleep loss, that is reversible following recovery sleep (Doran et al., 2001; Harrison & Horne, 1998; Harrison, Horne & Rothwell, 2000; Mullaney, Kripke, Fleck, & Johnson, 1983). This has been corroborated by findings that neuropsychological testing in healthy aging leads to a preferential impairment of the PFC (for a review see Hedden & Gabrieli, 2004), similar to those found in healthy young adults after sleep deprivation (Harrison et al., 2000). Brain imaging during performance on cognitive tasks when subjects were sleep deprived had illustrated activation of PFC regions (Dagher, Owen, Boecker, & Brooks, 1999; Diwadker, Carpenter & Just, 2000; Kroger et al., 2002; Mottaghy, Gangitano, Sparing,

Krause, & Pascual-Leone, 2002). Furthermore, imaging studies have demonstrated decreased prefrontal activation associated with decreased performance on arithmetic tasks during sleep deprivation, relative to following adequate sleep (Drummond & Brown, 2001; Drummond et al., 1999; Thomas et al., 2000). It has been suggested, however, that activation and deactivation of cortical regions may reflect task specific effects during sleep loss (Drummond & Brown, 2001; Drummond et al., 2000). In contrast to the arithmetic task, learning and divided attention tasks produced increased levels of cortical activation following one night without sleep compared to one night with sleep (Drummond & Brown, 2001). Moreover, a positive relationship between increased levels of sleepiness and increased prefrontal activation was reported. It is possible that this differential activation of the PFC may represent compensatory effort to perform under conditions that are not conducive to optimal performance (i.e., under prolonged wakefulness) and therefore characterize an adaptive cerebral response to the detrimental effects of sleep deprivation (Drummond & Brown, 2001).

One important factor that may influence the ability to perform neurobehavioral tasks is working memory and attention. It can be argued that without the ability to maintain either of these variables, neurocognitive functioning is severely impaired or impossible to achieve (Rogers et al., 2003). It has been suggested that a central executive, or central attentional system controls working memory (for a review see Baddeley, 2003). This may provide an explanation of why simple monotonous tasks that rely heavily on high levels of sustained attention and working memory are more sensitive to sleep loss than more complex tasks that require a higher level of cognition in addition to these basic functions. Brain-imaging studies have demonstrated a relationship between working memory and the PFC (Diwadker et al., 2000; McCarthy et al., 1994). Furthermore, the PFC has also been implicated in the maintenance of sustained attention (Rogers et al., 2003). Hence, the observed link between sleep deprivation and reduced neurobehavioral performance on prefrontal cortex- related tasks may represent impairments of sustained attention.

There is recent anatomical evidence that the central pacemaker located in the SCN plays a major role in the regulation of arousal and attention through noradrenergic mechanisms (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Aston-Jones, Rajkowski, & Cohen, 1999). Moreover, the SCN projects also to the PFC (Sylvester, Krout, & Loewy, 2002). According to the study by Sylvester et al. (2002), the SCN sends timing signals, via its relay in the paraventricular thalamic nucleus (PVT), to the medial PFC in rats. Assuming that a homologous circuit exists in humans, this pathway may modulate higher-level brain functions, such as attention, or working memory. This could explain the effects of circadian phase *per se* on neurobehavioral function and sleepiness, which have been reported in non-sleep deprived subjects during

forced desynchrony protocols (Wright Jr et al., 2002; Wyatt et al., 1999) and multiple nap studies (Cajochen et al., 2001; Lavie, 1986).

Impact of Circadian Phase and Time Awake on Sequence Learning and Planning

If circadian phase and time awake predominantly affect attentional aspects of neurobehavioral performance (i.e., sustained attention, working memory), then the question arises whether neurobehavioral tasks with low "attentional need" or tasks not so reliant on PFC function, are less susceptible to the effects of circadian phase and time awake. In fact, earlier studies reported differential time of day variations for different tasks under normal day-night conditions (for a review see Carrier & Monk, 2000). This has led to the conclusion that the best time to perform a particular task depends on the nature of the task (Folkard, Wever& Wildgruber, 1983). Besides the nature of task, it has recently been reported that the effects of time awake (Drummond, Brown, Salamat, & Gillin, 2004) and circadian phase (Bonnefond, Rohmer, Hoeft, Muzet, & Tassi, 2003) also depend on task complexity. However, other results suggest that when sufficiently controlled for masking of exogenous factors as during a CR protocol, there does not seem to be an interference of task complexity with circadian rhythmicity (Van Eekelen & Kerkhof, 2003). This confirms the need for controlling for environmental masking factors such as body posture, ambient light levels and temperature, food intake etc. not only for physiological circadian markers such as the core body temperature rhythm, but also when assessing the influence of circadian phase and time awake on neurobehavioral function. Therefore, we were interested whether under the strictly controlled conditions of a CR protocol, circadian and time awake effects are also apparent in short and stimulating tests with low attentional need - counter-intuitive to the common view that tests sensitive to time awake must be monotonous and simple. We have chosen to follow the temporal performance pattern in a short term (~3 min) maze tracing task throughout a 40-h CR protocol under low and high sleep pressure conditions. Differential sleep pressure conditions were achieved by depriving the subjects of sleep during the 40-h CR protocol (high sleep pressure condition) or by interspersing naps throughout the 40-h protocol (low sleep pressure condition, NAP protocol). First preliminary results indicate that planning time in the maze tracing task showed prominent decrements with time awake (for an individual example see Figure 4) under the high sleep pressure condition, which became apparent after ~15 hours of prior wakefulness- reminiscent to the reported effects on vigilance decrements measured by the psychomotor vigilance task (PVT) in our laboratory (Graw, Kräuchi, Knoblauch, Wirz-Justice, & Cajochen, 2004).

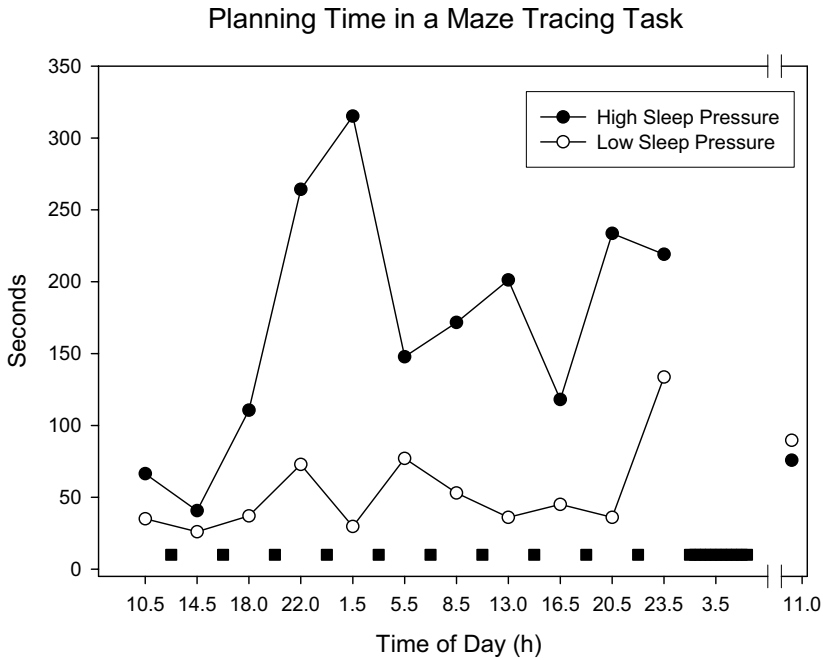

Figure 4. Time course of planning time during a 3-min mace tracing test for an individual subject under low- and high sleep pressure conditions in a CR protocol. The black boxes near the abscissa indicate the timing of the 75-min naps which were scheduled every 3.75 hours during the low sleep pressure protocol. The last time point represents planning time in the morning after the recovery night.

One night of recovery sleep (8 hours) after sleep deprivation was enough the reverse the deterioration in planning time back to normal baseline levels, as illustrated by the last data point in figure 4. It appears that extension of the wake episode into the biological night, i.e., after the evening rise of melatonin, is associated with marked decrements in planning time because the circadian pacemaker does not oppose the wake-dependent deterioration but instead promotes sleep at this circadian phase (Cajochen et al., 1999). Planning and prospective control are PFC-related cognitive functions (for a review see Miller & Cohen, 2001). Imaging studies have confirmed that planning performance in a maze tracing task significantly depends on the activation of the PFC (Petersen, Van Mier, Fiez, & Raichle, 1998). Our preliminary results confirm the hypothesis by Horne (1993) that such tasks are highly sensitive to the effects of elevated sleep pressure or sleep loss even though the maze tracing task was short lasting and rather stimulating for our study participants. Consequently, performance decrements in short term PFC-relat-

ed tasks associated with sleep loss may not be exclusively related to deficits in sustained attention. Interestingly, circadian effects on planning time in our maze tracing task were scarcely visible during the NAP protocol (Figure 4). This indicates that circadian phase and time awake may have differential effects on PFC- oriented tasks, such that circadian phase induces a general slowing of brain processes at the core body temperature minimum because of lower brain temperature levels not affecting short term planning performance. Time awake (40 hours of sleep deprivation), on the other hand, which in itself has no significant effects on core body temperature levels (Cajochen et al., 2001), affects predominantly frontal brain regions and leads to a "prefrontal tiredness" with all its consequences and among those deficits in planning capabilities.

In another approach we have tested the hypothesis whether neurobehavioral performance less reliant on the PFC shows also circadian and time awake effects. We have chosen a serial reaction time task (SRTT), where our study participants were naïve about a repeating pattern of sequences. They were exposed to a stimulus appearing at one of four horizontally separated locations on a computer screen, and were asked to press a spatially corresponding key as fast and as accurately as possible. Sequence learning forms the cognitive basis for behaviors like typing, musical performance, and route navigation. Researchers have described the acquisition of perceptual motor sequencing skills using either motor control (Hazeltine, Grafton, & Ivry, 1997) or learning and memory frameworks (Reber and Squire, 1998). Both explanations agree that distinct brain processes support explicit learning, which occurs with awareness, and implicit learning, which occurs without awareness. Therefore, sequence learning has implicit and explicit components which can occur simultaneously (Cleeremans & McClelland, 1991; Destrebecqz & Cleeremans, 2001).

Neuroimaging studies using an implicit SRTT with healthy adults have shown activation in the caudate, putamen (Peigneux et al., 2000; Rauch et al., 1997) and ventral striatum (Berns, Cohen, & Mintun, 1997). These findings have been confirmed in patients with striatal dysfunction who show an impairment on implicit SRTTs (Knopman & Nissen, 1991). For explicit SRTT learning, while striatal activation has rarely been noted, neuroimaging studies consistently find activation in cortical components of frontostriatal circuits, including the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, anterior cingulate, and dorsal and inferior parietal cortices (Hazeltine et al., 1997; Rauch et al., 1997; Willingham, Salidis, & Gabrieli, 2002). More recently, it has been reported that the hippocampus and related cortices are also involved in SRTT learning under both implicit and explicit learning conditions, regardless of conscious awareness of sequence knowledge (Schendan, Searl, Melrose, & Stern, 2003).

We have chosen to apply the same experimental conditions (40 hours of high and low sleep pressure conditions) to investigate performance and learning on the SRTT as we used for the maze tracing task. A SRTT of 5-8 min duration was applied 10 times in 3.75-h intervals throughout the 40-h CR- and NAP protocol. Unknown to the study participants, the sequential structure of the stimulus material was manipulated in such a way that within each SRTT pseudo-random sequences and a fixed-eight item sequence were applied. Some participants became aware of the repetitive character of some sequences in the course of the 40-h protocol, although they were unable to explicitly describe the sequence. We can therefore not conclude that we have tested solely implicit learning in our study, inferring that particularly striatal brain regions were activated during SRTT learning. However, we assumed

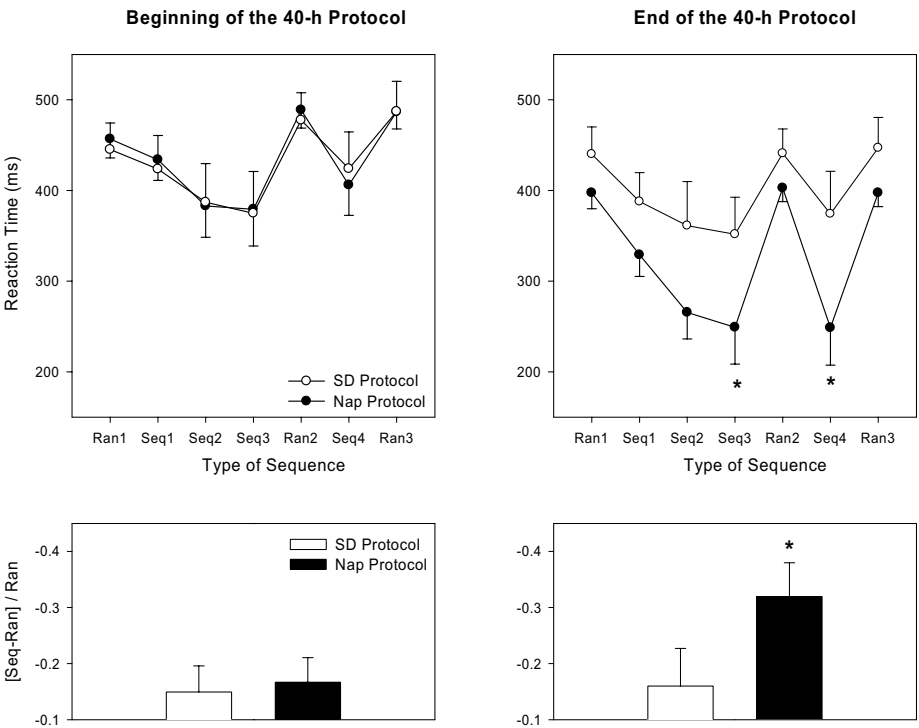

Figure 5. Upper panels: average median reaction time during the SRTT at the beginning and at the end of the sleep deprivation- (SD; high sleep pressure) and nap-protocol (low sleep pressure; n=8; ± SEM for both protocols). Ran 1–3: random blocks, Seq 1–4: blocks containing sequenced structures. Lower panels: learning to discriminate sequenced from random trials ([Seq - Ran]/Ran) at the beginning and end of the SD- and nap-protocol. The asterisk indicates significant improvement at the end of the low sleep pressure (Nap) protocol. According to Cajochen et al. (2004).

that the SRTT learning may have been less PFC- oriented than the maze tracing task used in our study. Indeed, performance on the SRTT did not deteriorate during 40-h of sleep deprivation (see Figure 5).

While reaction times during sequenced trials were significantly faster than during pseudo-random trials within the SRTT, they remained remarkably stable for both the pseudo-random and sequenced trials in the SD protocol. This was unexpected, since we hypothesized that reaction times particularly for the random stimuli would increase as a function of time awake in a similar fashion as reported for the simple reaction time task (PVT), due to impairments in sustained attention. One explanation could be that SRTT learning was not reliant on the PFC and therefore did not show detrimental effects of sleep deprivation. Another explanation could be that, since a total of 10 different (but formally equivalent) sequences were used in our study, participants learned sequence fragments that allowed them to react faster when exposed to new sequences that comprised these fragments. Since there were only four discrete locations on the computer screen for the stimulus to move, together with a high number of trials of the SRTT, the chance of getting the same fragments (i.e., subparts) of a sequence more than once was considerable. Indeed, we have statistical evidence that memorization of sequence fragments (i.e., chunks) may have helped the participants to learn new sequences faster (Cajochen et al., 2004). Under high sleep pressure our subjects experienced "prefrontal tiredness" with a resulting loss of prefrontal control in SRTT learning (i.e., being unable to efficiently memorize chunks). This would not lead to a deterioration on the SRTT during sleep deprivation, but the increased sleep pressure may have prevented the participants from efficiently retrieving chunks. We are currently in the process of validating this hypothesis by building a computation model of sequence learning based on the ACT-R framework (Wallach & Lebiere, 2003). According to this model, the retrieval probability of memory chunks encoding sequence fragments is a function of chunk activation. If the concept of "prefrontal "tiredness" can be mapped to memory activation in the ACT-R framework, sleep deprivation may result in weak memory traces that do not sustain over extended periods of time. Empirical evidence for this conclusion comes from the low sleep pressure protocol. In this 40-h protocol interspersed with naps of 75-min duration each, we observed a significant decrease in reaction time on the SRTT, which can be interpreted as SRTT learning (Figure 5). There was no "prefrontal tiredness" as indexed by waking EEG activity in the low frequency range during the low sleep pressure condition in the Nap protocol (Cajochen et al., 2001). Under these circumstances optimal and efficient learning and/or memorizing of chunks became possible. These explanations would imply that the PFC also plays an important role in sequence learning.

Another phenomenon we have observed during the low sleep pressure protocol was the fact that most of the improvement in SRTT learning occurred at specific time points during the 40-h protocol. There was a significant improvement particularly after naps abundant with rapid eye movement sleep (REM sleep). REM sleep is under strong circadian control (Czeisler, Zimmerman, Ronda, Moore-Ede, & Weitzman, 1980; Dijk & Czeisler, 1995; Zulley, 1980) with maximal REM sleep occurring in the morning between 6 to 10 am. Around this time of day the amount of REM sleep correlated with the improvement on the SRTT learning in our study (Figure 6).

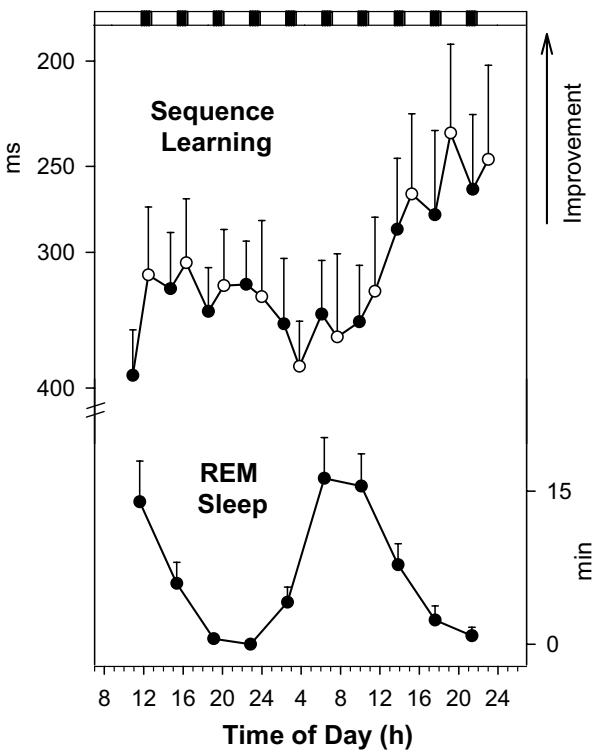

Figure 6. Upper panel: Average median reaction time (ms) sequenced trials (n=8; ± SEM) during the first presentation (filled circles) and second presentation (open circles) as they occurred relative to the timing of the naps (black shaded areas on the top abscissa) in the NAP protocol (low sleep pressure). Lower panel: Time course of the REM sleep amount (min) for each 75-min nap during the 40-h protocol. Time of day is expressed in hours. REM sleep significantly correlated with the over-nap learning in the naps (1, 2, 7, and 8). According to Cajochen et al. (2004).

This implies that at certain circadian phases, REM sleep may play a role in memory consolidation. Indeed, there is substantial evidence for REM "windows" in animal studies, where REM sleep episodes at certain times are the important times for memory consolidation to occur (for a review see Smith, 2001). Studies in humans also suggested the existence of a REM window at the end of the night sleep episode (Smith & Lapp, 1991; Stickgold, James, & Hobson, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000). Further evidence supporting the role of REM sleep in memory consolidation comes from a human functional imaging study, in which it has been shown that those cerebral brain areas which are involved in the execution of a SRTT are reactivated during REM sleep (Maquet, 2001; Maquet et al., 2000; Peigneux et al., 2003). In our study, however, we did not have direct evidence that the amount of REM sleep *per se* co-varies with the time course in sequence learning.

Remarkably, the time course of sequence learning for random and sequenced structures were both modulated by circadian phase (see Cajochen et al., 2004, figure 4). As predicted, reaction times were longer during the melatonin secretory phase (biological night) independent of the sleep pressure condition. This further confirms that circadian phase may have differential effects on neurobehavioral function than time awake or the level of sleep pressure.

Conclusions

Waking neurobehavioral performance related to sustained attention and short-term memory is regulated by a fine-tuned interaction of sleep homeostasis (i.e., time awake or asleep) and circadian rhythmicity. Misalignment of circadian rhythms and the sleep-wake rhythm leads to profound neurobehavioral decrements, which can become cumulative. We have also evidence that, under controlled CR conditions, circadian phase and time awake have a profound impact on performance on short lasting PFC-related tasks (i.e., planning) and sequence learning which comprises implicit and explicit components. Circadian rhythms and the sleep-wake cycle modulate neuronal functions which affect memory/learning processes.

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