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Circadian rhythms in cognitive performance: Methodological constraints, protocols, theoretical underpinnings

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Abstract

The investigation of time-of-day effects on cognitive performance began in the early days of psychophysiological performance assessments. Since then, standardised, highly controlled protocols (constant routine and forced desynchrony) and a standard performance task (psychomotor vigilance task) have been developed to quantify sleep–wake homeostatic and internal circadian time-dependent effects on human cognitive performance. However, performance assessment in this field depends on a plethora of factors. The roles of task difficulty, task duration and complexity, the performance measure *per se*, practice effects, inter-individual differences, and ageing are all relevant aspects. Therefore, well-defined theoretical approaches and standard procedures are needed for tasks pinpointing higher cortical functions along with more information about time-dependent changes in the neural basis of task performance. This promises a fascinating challenge for future research on sleep–wake related and circadian aspects of different cognitive domains.

Keywords: Neurobehavioural performance; Sleep deprivation; Circadian rhythm; State instability; Task difficulty and complexity; Inter-individual differences; Ageing

1. Introduction

The effects of time of day and extended episodes of forced wakefulness on cognitive performance have been investigated since the beginnings of experimental psychophysiology in the late 19th century. These early studies were mainly concerned with determining the most favourable time of day for teaching in order to optimise school timetables. The first systematic link between cognitive performance, chronobiology and sleep was made by Nathaniel Kleitman, the pioneer in circadian and sleep research. He noticed a diurnal variation in speed and accuracy of cognitive performance with best performance in the afternoon and poorest early in the morning and late at night [1]. Moreover, he observed that this variation appeared to be dependent upon the diurnal rhythm in body temperature, and that a spontaneous or induced change in body temperature was reflected in a change of reaction time in the opposite direction (i.e. an increase in body temperature provokes a decrease in reaction time and *vice versa*; [2]). Kleitman postulated that the parallelism between the diurnal rhythm in body temperature and time-of-day effects in performance could reflect a causal relationship. Besides reaction times, he also investigated more complex performance measures such as card sorting, mirror drawing, code transcription and multiplication speed, which all showed a consistent temporal relationship with the diurnal rhythm of body temperature and heart rate (Fig. 1) [1]. As the existence of self-sustained endogenous circadian rhythms in humans was not yet established at that time, Kleitman assumed that the diurnal rhythm in body temperature might be brought about by a diurnal rhythm in the tonicity of the skeletal musculature. Accordingly, he concluded that accuracy and speed in performance would depend on the level of muscle tonicity and in turn on the metabolic activity of the cells of the cerebral cortex. By raising the latter through an increase in body temperature one can indirectly speed up thought processes [2].

It took another 40 years before Aschoff and Wever clearly demonstrated that those diurnal rhythms in *psychological data*, as they termed them, were clearly related to the circadian system in humans. In a 28-h forced desynchrony protocol (see below)

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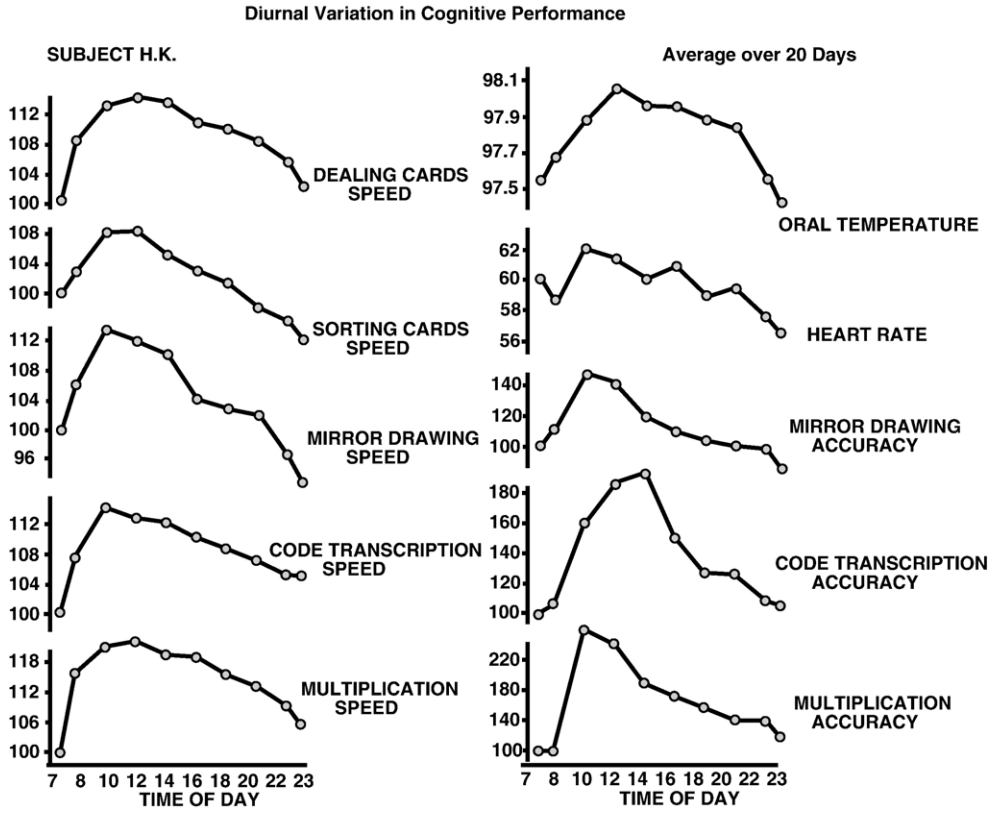

Fig. 1. Diurnal variation in speed and accuracy of performance, expressed as the reciprocals of the ratios of the time it took to perform a task and the number of mistakes made to the time and the mistakes made in the first series of tests at 7 a.m., at which hour the speed and accuracy of performance are taken to be 100. One subject, 10 trials daily, the average of 20 days. Redrawn with permission from [1].

they quantified the period of the "circadian performance rhythm" for the first time (i.e. 24.8 h, running synchronously with the overt rhythm of rectal temperature). Moreover, their periodogram analyses yielded not only this 24.8-h component but also a prominent 28-h component for the performance measure "computation speed" (Fig. 2) [3]. This was the first evidence that both the circadian system and the imposed sleep–wake cycle (i.e. duration of prior wakefulness in this case) contribute about equally to the variation in a cognitive performance measure. This evidence was confirmed, another 40 years later, by Wyatt et al. [4], who quantified circadian and sleep–wake homeostatic aspects in a variety of neurobehavioural performance measures during a 20-h forced desynchrony protocol (Fig. 3) [4]. In addition, two studies [5,6] were aimed at assessing whether the influence of body temperature on performance is independent of circadian phase. The findings demonstrated that an increased body temperature, independent of internal biological time, is correlated with improved performance and alertness, supporting Kleitman's postulate of a causal role for body temperature on performance [5,6]. However, it is unlikely that performance is directly and solely mediated by changes in body temperature. Since the execution of all performance tests requires a certain degree of attention, a variety of factors besides external and internal changes in body temperature must modulate performance levels. As it is more difficult for a tightrope artist to keep his or her balance in the middle distance between the two suspension points, so it is more difficult to keep attention in the middle of the night at the minimum of core body temperature (CBT). However, it is not the length of the rope that directly and solely influences the artist's capacity to keep his or her balance; it is rather the compensatory effort of brain centres responsible for keeping balance that is the more important. Similarly, it may be more difficult to allocate cognitive resources away from the default brain network [7] to the brain regions required by a given task demand during the circadian CBT minimum.

In the following sections, we will review and summarise factors, complexities, and potential pitfalls that need to be considered when investigating human circadian performance rhythms.

2. Cognitive performance and methodological constraints

Cognitive performance subsumes behavioural responses to tasks of different complexity, challenging psychomotor reactivity up to higher cognitive functions (i.e. memory, language, and executive functions). It is clearly differentiated from, but correlated with, mood states, fatigue (defined as "loss of desire or ability to continue performing"), and subjective sleepiness ("desire to sleep") [8]. From a methodological point of view (apart from technical methods), assessing circadian rhythms in human performance is more complex than measuring the circadian rhythm of CBT or the pineal hormone melatonin. Since for the latter the effects of confounding "masking" factors

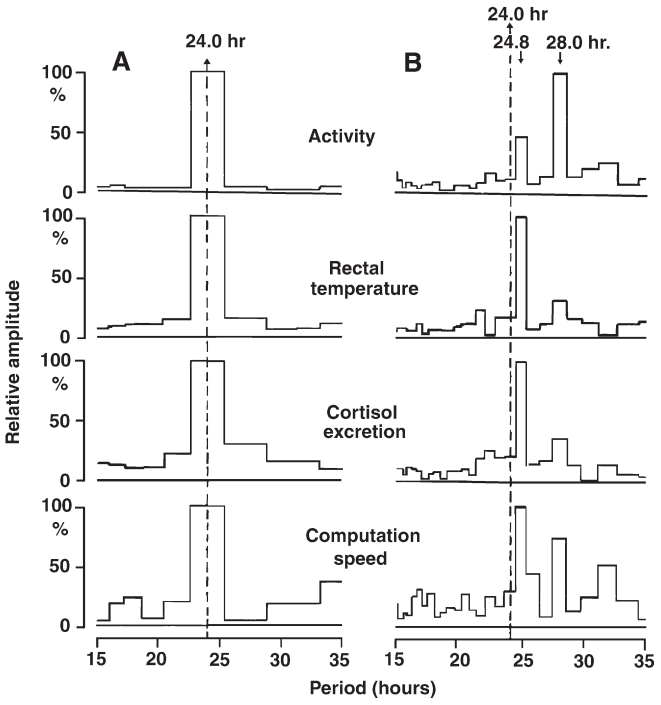

Fig. 2. Periodogram analysis of the time series of activity, rectal temperature, cortisol excretion and computation speed under (A) entrained 24-h conditions and (B) during a 28-h "day". With permission from [125], p. 165.

such as light and body posture are known, standard operating procedures have been developed for how to measure this circadian marker, in particular the "dim light melatonin onset" [9]. Two main sources of masking appear to be relevant when one tackles the problem of assessing human cognitive performance rhythms: the kind of task used (i.e., low *vs*. high cognitive load, task duration, self *vs*. not self-paced, etc.) and inter-individual differences in task performance. In other words, both the task itself and the subject population studied have a major, probably the most important, impact on the measured output variable, such as reaction time. This is not trivial, since it can lead to a very poor signal-to-noise ratio that makes the measurement of underlying endogenous rhythms near-impossible. Furthermore, assessing rhythms requires repeated sampling of a given parameter across time (i.e. a time series). For most tasks, this poses a problem since multiple measurements are not independent of each other, and carry-over, practice, learning, etc. effects impact on the underlying circadian oscillation. Particularly vulnerable tasks are those related to the prefrontal cortex (PFC). This brain region is specialised in generating and executing novel goal-directed behaviour. Thus, an especially important aspect of these tasks is novelty. However, repeated task administration leads to familiarity and routine. Consequently, the functional involvement of the PFC diminishes and shifts towards lower sensory and motor cortical regions [10].

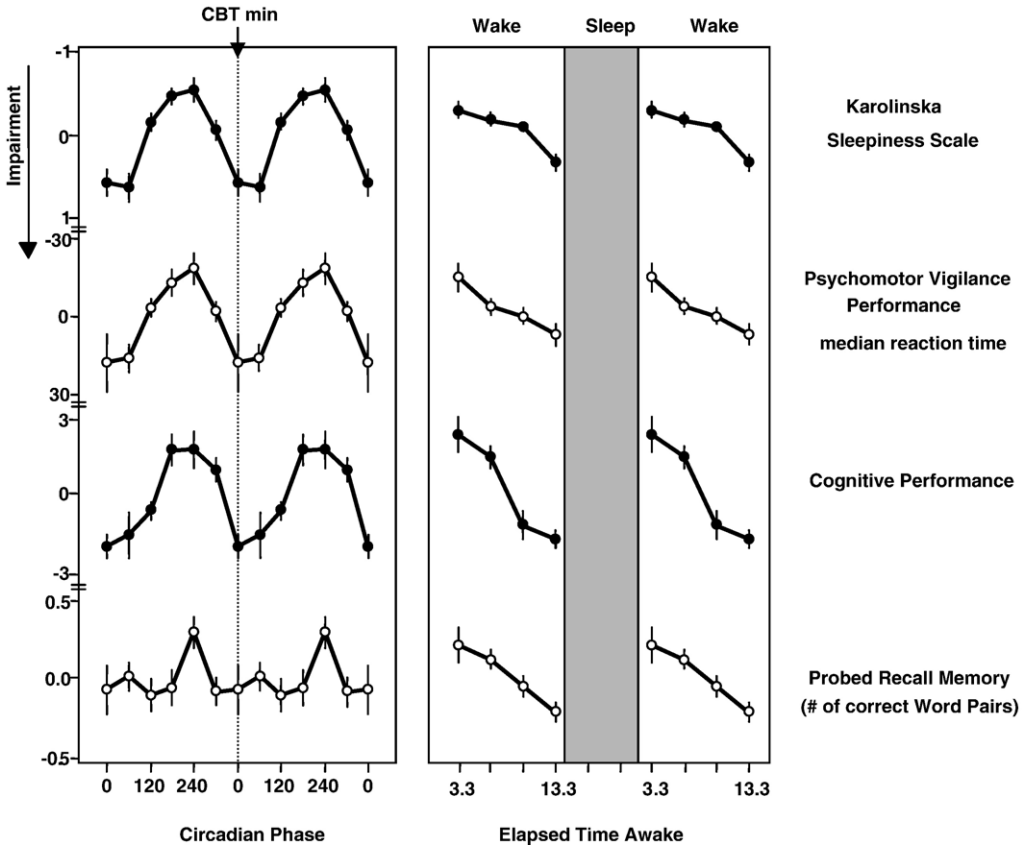

Fig. 3. Double plots of main effects of circadian phase relative to minimum of CBT (left) and duration of prior scheduled wakefulness (right) on neurobehavioural measures. Plotted points show deviation from mean values during forced desynchrony section of protocol and their respective S.E.M.s. For all panels, values plotted lower in panel represent impairment on that neurobehavioural measure. Redrawn with permission from [4].

2.1. Task complexity

At the first glance, it would seem that task complexity does not play a crucial role for its applicability in circadian and sleep research. The widely used psychomotor vigilance task (PVT) [11], highly sensitive to circadian- and sleep loss-related performance decrements, can hardly be considered complex. More complex tasks such as those testing executive functions are also likely to be sensitive to sleep loss and circadian phase. Executive functions notably include the ability to plan and coordinate willful action in the face of alternatives, to monitor and update action as necessary and to suppress distracting material by focusing attention on the relevant information (i.e. inhibition). In particular, PFC-related tasks that are relatively complex (i.e. Tower of London, Wisconsin Card Sorting Test, logical reasoning task) have been shown to be sensitive to effects of time of day and sleep loss [12,13]. However, a task supposedly challenging a certain cognitive function (e.g. response inhibition) can lead to different results depending on the sensory modality tested or on the paradigm used (i.e. go/no go or Stroop task). Indeed, the results of one of the most widely used neuropsychological tests to study attention and, notably, its inhibitory processes, the Stroop Colour-Word test [14], are not consistent; some show effects of sleep deprivation and time of day [15,16] and some do not [17,18]. One explanation for these divergent results is that executive control is not a unitary process but rather related to independent processes [19], and that sleep deprivation and time of day appear to affect these components selectively [20].

Furthermore, a function challenged in a given test may allow different performance strategies, which may vary in a circadian manner [21]. Consequently, tasks requiring complex performance skills are more difficult to interpret in terms of the underlying differentiated cognitive processes.

2.2. Measured variable

Tasks with the stimulus-response approach (see below) had been classified either as “self-paced” or as “experimenter-paced”. In the latter, subjects respond to stimuli presented by the experimenter whereas in self-paced tasks the subjects determine stimulus appearance. However, two different administrations of one and the same task evoke different performance strategies. In experimenter-paced tasks, subjects perform under sleep deprivation at the expense of performance accuracy in order to keep up with the speed of stimulus appearance. In self-paced tasks sleep-deprived subjects perform more slowly, but they successfully avoid errors [22]. To measure errors in self-paced tasks and speed in experimenter-paced tasks would therefore be unreasonable, which demonstrates that dependent variables have to be chosen carefully in order to be meaningful for interpretation of test results.

2.3. Task difficulty and duration

Sleep- and circadian rhythm-related effects on performance in neuropsychological testing are most likely smaller than those detected in lesion studies. Therefore, a clinical task normally used in diagnostics will probably evoke a ceiling effect in an experimental setting with healthy volunteers and multiple testing. On the other hand, a task proving to be too difficult will challenge the endurance of a subject to concentrate and to resist distraction rather than the originally aimed cognitive ability [23]. Therefore, in order to meet the subject’s ability to perform on the one hand, and to avoid a ceiling effect on the other, it is recommended to employ versions of a given task with different degrees of difficulty. In one of our studies looking at planning performance, we employed two difficulty levels in a maze-tracing task and could show that only the more difficult version of the task was able to reveal circadian rhythmicity and sleep loss-related decrements (Fig. 4) [24].

Task duration plays a crucial role with respect to endurance and habituation to stimulus salience (and, consequently, distractibility by irrelevant environmental stimuli). Wilkinson recommended the use of relatively long duration vigilance tasks (i.e. 30–60 min) to observe effects of sleep deprivation [25]. However, more recent studies (10-min PVT; [26]) and our observations (5-min PVT; 3-min maze tracing; [24,27,28]) indicate that circadian- and sleep loss-related decrements in performance can also be reliably quantified with short-duration tasks.

2.4. Practice effect

In order to detect time-of-day effects it is essential to assess performance over the 24-h cycle. However, multiple testing leads to an increase in the respective proficiency, which confounds the effects of the independent variable(s). It is assumed that the learning curves of different tests generally have an asymptotic course [29,30] with different slopes. Unfortunately, this problem is well known and very often mentioned, but rarely eliminated. It is true that together with all the other unknown task-dependent influences (see above) it is difficult to distil out a pure experimentally-induced effect on task performance, but ignoring it hinders the development of a reliable picture of sleep loss and time of day-related cognitive impairments.

There are three possible ways to tackle this problem: these are firstly by training subjects up to the asymptotic practice level before experimental testing, and secondly by a balanced design which needs a high sample number (subjects in different order over times of day, then averaging each test session over subjects). A third possibility is described in our study where we looked at sleep loss-related decrements in planning performance in healthy elderly [24,28]. By means of subtraction of the learning curve, which had been determined beforehand in a control group, this can be disentangled from the measured performance curve. This method can be applied to any task and allows actual determination of the increase in proficiency. Despite the need to have a control group, the required sample size is still smaller than in a balanced design. However, even with control of the learning curve, one must not be deceived by the fact that the nature of cognitive processing may change over repeated task sessions [10].

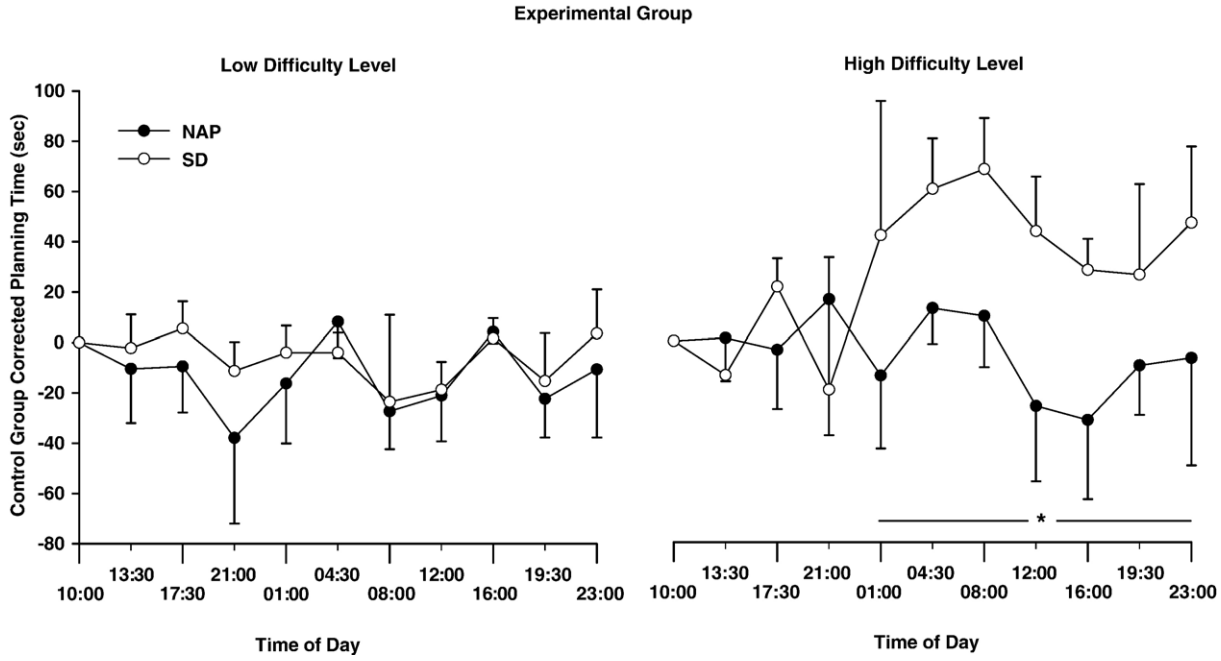

Fig. 4. Maze tracing performance (mean control group adjusted planning time in seconds) in low (left panel) and high (right panel) difficulty task versions during sleep satiation (NAP) and sleep deprivation (SD). Only for the high difficulty level were statistically longer performance times in the SD condition than in the NAP condition present ($p < .05$). The line with asterisk indicates the significant difference between the two conditions on day 2 (t-test with data pooled for each day). Bars indicate S.E. M. With permission from [24].

2.5. Inter-individual differences

There are marked inter-individual differences in several important circadian and sleep-related aspects of physiology, such as circadian period length (tau, ranging from 23.9 to 24.5 h) [31], circadian phase or "chronotype" ("larks" or "owls", referring to behavioural preferences of morningness and eveningness) [32–34], sleep duration [35], vulnerability to sleep loss (which, remarkably, is independent of individual sleep need [36]), most of which change with age [37] as well as personality traits (introversion and extraversion) [38].

Individual variability in waking neurobehavioural functions of healthy adults has attracted considerable scientific interest, studied both under normal conditions and during sleep deprivation. However, the relationship between individual differences in waking functions and individual differences in sleep physiology has hardly been examined. Recently, inter-individual differences in the vulnerability to sleep loss have been reported from different laboratories [39–41]. These studies have revealed that individuals differ in the magnitude of sleepiness and cognitive performance impairment during sleep deprivation – by as much as an order of magnitude – and that this individual variability is highly replicable over repeated exposures to sleep deprivation (reviewed in [42]). Furthermore, although not based on repeated observations, Frey et al. could show that during sleep deprivation individual vulnerability to performance impairment varied depending on the task examined [40]. Van Dongen et al. went so far as to coin a new expression based on the Greek word "trotos" for vulnerability, and in line with the terms "chronotype" and "somnotype," this phenotype may be referred to as "trototype". Individual differences in responses to sleep loss have been observed not only during acute total sleep deprivation but also under conditions of chronic sleep restriction [41]. In the future, it will be useful to investigate if individual differences in vulnerability to sleep loss covary with individual differences in basal sleep need and/or baseline sleepiness/alertness. This could clarify if individual differences in vulnerability to sleep loss play a role in the existence of naturally sleepy and alert individuals.

At present, it remains largely unknown what factors underlie or even predict circadian and sleep/wake-related traits, what relationships these traits may have to each other, and what functional significance may be associated with specific traits (for a comprehensive review, see [42]).

2.6. Ageing

Regarding cognitive functioning, changes are generally manifested from the age of about 60 years and characterised by gradual cognitive slowing and memory loss, which is related to structural and functional changes in the PFC (fronto-striatal functional loop) and the medial temporal lobe [43,44]. Sleep-related changes are associated with decreased consolidation of nocturnal sleep (decreased slow wave sleep and EEG slow-wave activity), increased daytime napping, and earlier sleep-onset and -offset [45–49]. The majority of older people are morning-types (75%) in contrast to only 7% of young adults [52]. However, the advanced sleep phase cannot be explained by a general phase advance of the circadian timing system (measured by the urinary melatonin metabolite, MT6s) [50], but is more likely due to a failing transduction of the circadian signal downstream from the circadian timing system [51].

Investigations of the circadian modulation of cognitive functioning have revealed that whereas performance of younger adults improves over the day, in older subjects it deteriorates [52], suggesting that optimal performance is achieved when subjects are tested at the preferred times of their respective chronotypes [53]. Consequently, age-related differences appear most marked when older subjects are tested at non-optimal times of day [54]. Concerning sleep-related cognitive changes, Carrier and Monk reported that, in older subjects, the sleep-homeostatic influence on performance regulation is stronger than that of circadian processes [55]. Nevertheless, several studies have shown that the detrimental effect of sleep loss is actually smaller in the elderly than found in young subjects [56–60].

In one of our studies we investigated age-related performance changes in the PVT with respect to the circadian timing system (constant routine protocol, see below) and the sleep homeostat (sleep satiation *vs*. sleep deprivation) [28]. The number of our subject groups permitted analysis of the data also with regard to gender-specific differences. Women had slower reaction times, independent of their age, which we interpreted as a difference in performance strategy (they avoid making mistakes). The age-related differences in reaction time occurred most markedly under low to moderate levels of sleep pressure and gradually diminished under high sleep pressure conditions and during the nighttime (Fig. 5) [28]. This means that although, under normal sleep–wake conditions, older people are slower, surprisingly, under sleep deprivation or during the circadian trough, they are not worse than the young. Our results showed an attenuation of the circadian cycle amplitude in the elderly, suggesting a generally weaker circadian regulation at the physiological level. We argued for this interpretation with evidence from sleep physiology data acquired in the same study [45,61,63].

This listing of methodological constraints illustrates the difficulty of performance assessment in circadian and sleep research. Considering them makes the importance for a well-reflected and appropriate choice of dependent variables and statistical analyses clear. Moreover, there are some recommendations of how tests should be constituted in order to be suitable for investigations in this field [64,65]. However, the demands are undoubtedly met for only one test, implemented and approved in many chronobiological studies, namely the PVT.

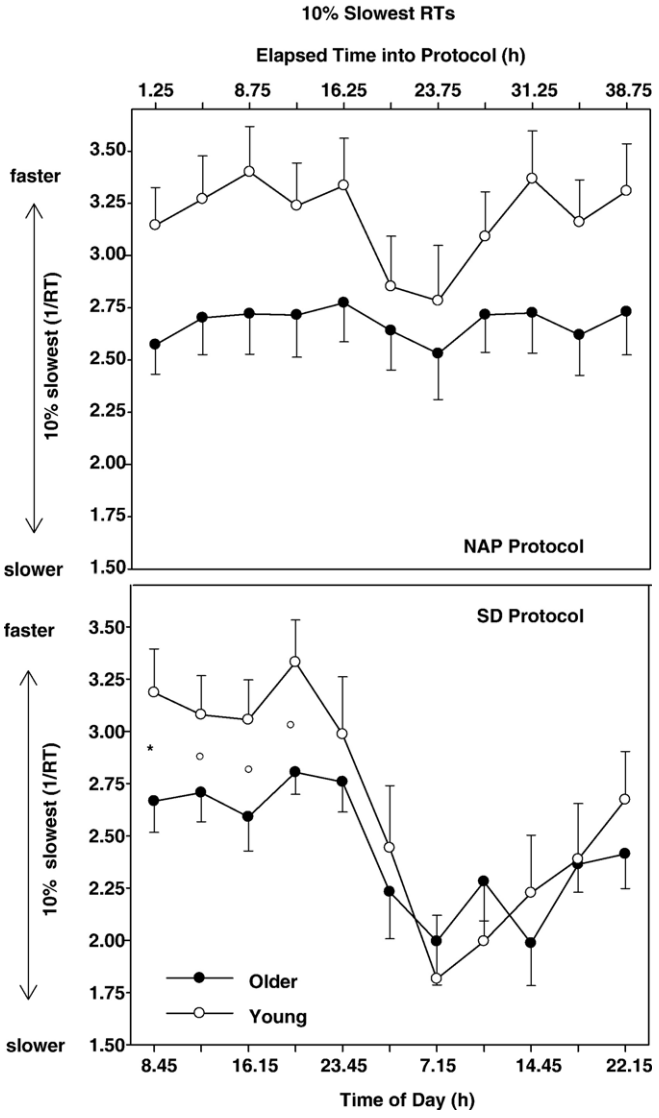

Fig. 5. Vigilance performance exemplified by the slow reaction time domain (10% slowest RTs) in a young and older group under low (NAP) and high (SD) sleep pressure conditions. Asterisk indicates a significant difference; circles indicate a tendency in post-hoc comparisons (Curran Everett's alpha-corrected *t*-test). With permission from [28].

3. Quantifying circadian and wake-dependent effects on cognitive performance

Two key phenomena characterise sleep in humans and mammals in general: first, sleep occurs at specific times of the day and, second, the longer we lack sleep the more difficult it becomes to resist it. However, even after several hours beyond our regular waking time, we experience fluctuations of sleepiness/tiredness (e.g. temporal waves of less or more tiredness). These three statements reflect a phenomenon which is based on two synchronous and opposite mechanisms: the homeostatic drive for sleep (process S) and a circadian clock-like process (process C), both also described as systems (the sleep homeostatic system and the wake-promoting system, respectively) and subsumed in the two-process model of sleep regulation [66,67].

This model, originally developed to predict sleep regulation, has increasingly been applied to estimate human performance, which also is modulated by the two processes S and C. Process S is defined as the homeostatic sleep promoting process. It continuously accumulates during time awake, concomitant with a decrease in waking cognitive performance and alertness and an increase in sleepiness/fatigue. During sleep, particularly non-REM sleep, process S continuously decreases [68]. Therefore, S represents an hourglass process, accumulating during wakefulness and dissipating during sleep. On the other hand, process C, the circadian process, oscillates with a period of about 24 h. It represents a clock-like process independent of whether the person is asleep or awake that is normally synchronised with

external time (i.e. time of day). Process C represents a wake-promoting drive to balance the accumulating homeostatic drive for sleep during wakefulness (Fig. 6) [69].

Little is known about the brain structures involved in process S, and it seems that not only one but also several neural correlates for S exist [70]. On the other hand, process C is controlled by a concrete brain region, the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus (for a review, see [71]). The SCN is the master circadian pacemaker, which drives the temporal circadian organisation of different processes from genes to behaviour. Thus, clock genes encode circadian time in a way that temporal programmes for the whole organism are manifest, as, for example, the CBT rhythm and the release of the hormones melatonin or cortisol. How exactly process C exerts its influence on process S is still unresolved. However, there is recent evidence from anatomical studies that arousal systems located in the brain stem, basal forebrain and hypothalamus, are under both homeostatic [72–75] and circadian control [76,77].

With increasing time awake, particularly beyond the habitual amount of time spent awake (ca. 16 h), cognitive performance degrades considerably. Interestingly, to recover optimally from sleep loss-related performance decrements, less sleep is actually needed than the absolute hours of sleep formerly lost. This indicates that sleep *per se* exerts a fast acting recovery function to restore normal performance [78]. Which aspects of sleep (e.g. slow wave sleep, sleep spindles, REM sleep) play the most important role in this recovery process is not yet clear.

The circadian modulation of cognitive performance shows a close temporal association with the circadian rhythm of CBT

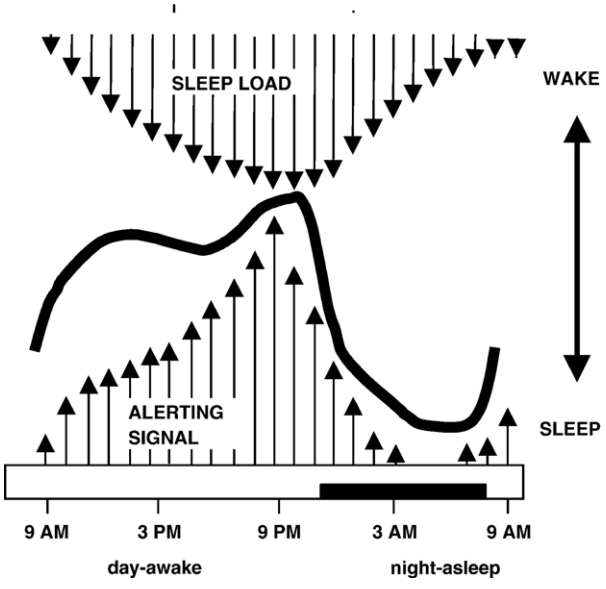

Fig. 6. Schematic figure of the "opponent processes" mediating physiological sleepiness as a function of time of day. Sleep load increases in response to wakefulness imposed and/or maintained by the pacemaker in the SCN. Increasing levels of SCN-dependent alerting signals over the subjective day opposes homeostatic sleep drive, both of which peak shortly before the habitual sleep phase. Redrawn with permission from [69].

with its maximum in the evening and nadir in the early morning (see Kleitman, above, and, for a review, [79]). This association is even more pronounced with escalating drive for sleep [80], which itself demonstrates that the interaction between C and S is non-additive [81], an assumption which has been recently confirmed by a new model [82].

To allow for sleep inertia, a transitional state of lowered arousal experienced upon awaking from sleep, the two-process model was expanded with a process W [83]. Sleep inertia has been shown to exert a detrimental effect on cognition for from 1 min up to 4 h post-awakening, depending on prior sleep [84]. Thus, it is closely related to processes S and C and should not be underestimated in its impact on cognitive performance [85].

In order to unravel the nature of circadian and sleep-dependent influences on physiological and performance rhythms, it is necessary to disentangle the two interacting processes by designing appropriate study protocols.

3.1. Constant routine protocol (CR)

A crucial factor in circadian research represent the so-called "masking" influences. Any external (e.g., body posture, food, light) or internal factor (e.g., stress level, digestion, motivation) has the potential to mask the "true" endogenous rhythm of, for instance, CBT or melatonin. Therefore, rhythmic clock outputs, whether physiologic or cognitive behavioural in nature, require strong control over all other possible exogenous cues in order to avoid their masking influences on the measured variables. An appropriate setting has been developed under conditions without time cues, in which all known and relevant masking factors are held constant and reduced as much as possible [86,87]. In the CR protocol, participants are subjected to a regime of more than 24 h of wakefulness in dim light. Subjects stay in a semi-recumbent position. Hourly isocaloric snacks provide a constant energy supply. However, there is no desynchronisation between the sleep–wake cycle and the circadian pacemaker — which consequently does not allow separation of these two processes in CR protocols. Therefore, the effects of prolonged wakefulness (>24 h) are superimposed on the circadian profile of various performance variables [8,55,88–92]. Since cognitive performance is modulated by both processes S and C, the time course of any task variable measured reflects the interaction of these processes during a CR and, depending on the task, exhibits a more "circadian" or a more "homeostatic" pattern.

In addition to classical CR protocols, we and others have used multiple nap protocols under the same demasking CR conditions [24,28,89,93,94]. The advantage of these so-called ultra-short sleep/wake cycle protocols is that the homeostatic build-up of sleep pressure is kept very low by the intermittent sleep opportunities (provided they are long enough). We have quantified this by subjective sleepiness ratings and frontal low-EEG activity, a good measure of process S during wakefulness [89]. Therefore, one can "demask" (although , not completely) circadian oscillations from impeding homeostatic influences, which results in more "circadian" profiles for cognitive performance measures [24,28] than does the classic CR protocol.

3.2. Forced desynchrony protocols

Under normal, so-called entrained conditions, the circadian rhythms of various physiological and cognitive functions as well as the sleep–wake cycle are synchronised with each other and with the diurnal day–night cycle. The timing of sleep and wakefulness is such that the main sleep episode in humans usually starts on the falling limb of the CBT rhythm, while sleep termination in the morning coincides with the rising portion of the CBT rhythm [95]. Light is the major synchroniser for the endogenous circadian pacemaker in the SCN. It synchronises circadian rhythms to the 24-h earth rotation such that we entrain to the natural light–dark cycle. This is necessary since most people have endogenous periods longer than 24 h [31]. The sleep–wake cycle can also spontaneously desynchronise from the CBT rhythm and exhibit rather long (up to 48 h) or rather short (<24-h) rhythms. This so-called spontaneous internal desynchronisation occurs usually after two weeks under time isolation and low light levels [98]. However, it can also be forced by scheduling subjects on extreme sleep–wake schedules, which deviate considerably from the 24-h rhythm. In other words, the imposed sleep–wake cycle lies outside the range of entrainment of the biological clock. Thus, the endogenous circadian pacemaker cannot keep track with the imposed extreme sleep–wake cycle (e.g. 28 h) and starts to follow its own rhythmicity (i.e. "free runs"). Under conditions of low ambient light levels or no light (i.e. totally blind people), this synchronisation or entrainment is no longer achieved. Circadian rhythms start to oscillate at their own endogenous period, which is called a "free run". The relationship to the sleep–wake cycle alters, such that sleep begins at the CBT minimum and ends at its maximum. Thus, the phase angle between the circadian CBT rhythm and the sleep–wake cycle changes [96,97]. Nathaniel Kleitman 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 already realised 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 desynchronisation 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 h (see [99]). As explained above, the circadian rhythms could not be entrained to the new imposed day length, but continued to oscillate with their endogenous period. This protocol has later been termed the forced desynchrony protocol. In these protocols, scheduled sleep and wake episodes occur at virtually all circadian phases (Fig. 7). Since subjects are scheduled to stay in bed in darkness, the variation in the amount of wakefulness preceding each sleep episode is minimised. It is thus possible to average data either over successive circadian cycles or over successive sleep or wake episodes and thereby to 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 (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 has been demonstrated by the findings 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 h) and with markedly different levels of physical activity [4,31,100]. So far, forced desynchrony protocols have been 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 [101]). More recently, quantitative aspects of circadian and homeostatic

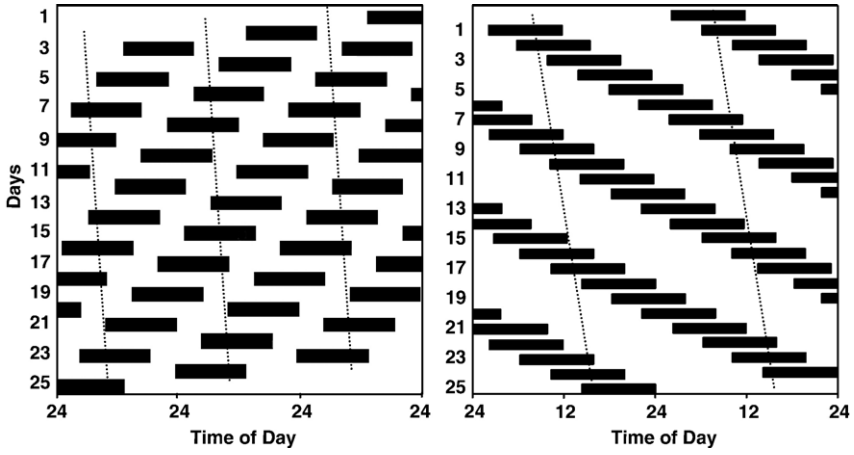

Fig. 7. Left-hand panel: Triple-raster plot of a 25-day forced desynchrony protocol. Each successive 24-h period is plotted next to and beneath each other. In this example, habitual bedtime was at 2400 h and habitual wake time at 0800 h. After three baseline cycles of 24 h (not included in the figure), 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 lx) and asleep for 14.28 h (light <0.03 lx). 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.

regulation of neurobehavioural function during forced desynchrony have also been reported [4,6], reviewed in [102].

4. Cognitive performance and circadian rhythms and sleep: theories and hypotheses

Three experimental approaches can be classified: a "stimulus-response approach" to measure behavioural alertness [64], an "executive function approach" dealing with PFC-related functions, and a "memory approach" illustrating the beneficial role of sleep. From early on, sleepiness has been related to time of day (Michelson, 1897, cited in [103]) and is obviously co-varying with mental performance. As a matter of fact, any performance parameter being affected by sleep loss also shows, in general, a circadian rhythm and *vice versa*. Therefore, theoretical approaches to sleep-related and circadian-modulated performance phenomena cannot clearly be classified as being derived either from sleep research or from chronobiology research. They refer more to the description of phenomena than to the explanation of their underlying processes. Also, in recent research, the investigated cognitive domains cannot be categorised as typically belonging to either sleep or circadian studies (for an exhaustive list of tests, see [79]).

The memory approach has become increasingly popular in the past 5 years. In general, brain circuits are thought to be remodelled (i.e. synaptic reorganisation/neural plasticity) during sleep following exposure to stimuli during wakefulness [104,105]. Procedural, implicit, and non-declarative memories are reported to be facilitated by subsequent REM sleep, while declarative and explicit memories are considered to be facilitated by subsequent non-REM sleep (for a review, see [106]). The role of the circadian system in memory consolidation and improvement in performance is less well understood. We have reported that sequence learning was modulated by circadian time across sleep deprivation and improved following naps abundant with REM sleep occurring after the CBT minimum [107]. In a recent study, cognitive and vigilance performance was tested while subjects lived in the laboratory for over a month [30]. Half of the subjects tested maintained a normal relationship between the sleep–wake cycle and internal circadian time (synchronised group), whereas the other half did not (not-synchronised group). The results clearly showed that a proper alignment of the sleep–wake cycle and internal circadian time is crucial for enhancement of cortical performance [30].

The executive function approach was conceptualised by Horne et al. who postulated a link between waking function of the PFC and the frontal predominance of EEG delta activity in sleep [43,108–110]. Since then, it has been shown in many studies that cognitive functioning related to the prefrontal cortex is particularly vulnerable during sleep loss (for a review, see [79]). This finding has been corroborated in numerous brain-imaging studies demonstrating altered prefrontal activation associated with decreased performance during sleep deprivation relative to adequate sleep [12,111–115].

The stimulus-response approach using the PVT dominates sleep-related and circadian studies. This measure has substantially contributed to the formulation of testable hypotheses and the unification of results in a theoretical context as is delineated in the following section.

4.1. Arousal theory

As explained above, time spent awake and circadian timing influence performance, and it appears that its rhythmicity is not directly caused by corresponding mood and physiology rhythms (e.g. CBT), as formerly suggested by Williams et al. [116] and Kleitman [99]. In the arousal theory of time-of-day effects, circadian performance variations are postulated to reflect an underlying circadian rhythm in basal arousal level [117]. Phase differences between types of task led to a discussion whether there exist several biological clocks manifested in different performance rhythms [103]. However, more recent studies suggest that inter-task differences in circadian rhythms may fail to appear when data collection is extended into the night (CRs, [88,90,92]) and when subjects not deprived of sleep are tested at all circadian phases (forced desynchronisation protocols, [4,6]). Also, with regard to biological fitness, it has to be questioned whether the redundancy of several rhythms makes sense. The phase differences in task types could as well be explained by other factors as discussed in the next section.

4.2. Lapse hypothesis

The predominant explanation in the past 45 years for sleep loss-related performance decrements has been the "lapse hypothesis" [116]. A sleepy participant is thought to perform normally until a "microsleep" (i.e. short periods of low arousal characterised by a typical EEG-pattern: alpha-wave depression and emergence of slow-wave activity) occurs, causing the incidence of a lapse (i.e. reaction time greater than twice the subject's baseline mean). These lapses, later also called "errors of omission", are a characteristic feature of a sleepy person. Optimal performance on the PVT appears to rely on activation both within the sustained attention system and within the motor system, and poor performance during sleep deprivation may result from a disengagement from the task and related inattention. Brain regions responsible for this are localised within midline structures and have been shown to be involved in the brain's "default mode" [115].

The lapse hypothesis [23] did not take into account that between the occurrence of lapses reaction times generally showed a greater variability with increasing time spent awake. Thus, the concept of lapsing cannot fully explain cognitive impairment induced by sleep loss. Notably, the variability in PVT performance reflects a combination of normal timely responses, errors of omission (i.e. lapses), and errors of commission (i.e. responding when no stimulus is present).

4.3. State instability hypothesis

The "state instability hypothesis" addresses the issue of the general appearance of increased performance variability (not only of lapses) and explains it by the progressive dysregulation of sleep-initiating and wake-maintaining mechanisms. Thus,

state instability is evident in the waxing and waning of attention and arousal over time (i.e. milliseconds to minutes), especially during episodes of sleep deprivation [91]. It also considers the fact that with longer time spent on task (i.e. within a given test bout), performance becomes more variable, which induces compensatory mechanisms leading to errors of commission (premature reactions). Depending on the degree of sleep deprivation, the fastest reaction times on the PVT do not change or change only modestly relative to the well-rested state, which reflects the fact that individuals experience instances of relatively normal attention and arousal levels even when sleep deprived [27]. On the other hand, the slowest reaction times can lengthen dramatically after sleep deprivation, reflecting instances when individuals experience markedly reduced levels of attention and arousal [27,91]. Using functional magnetic resonance imaging to study the neurophysiologic correlates of fast and slow reaction times on the PVT following 36 h of sleep deprivation, it was shown that fast reaction times are supported by increased activation within a sustained-attention network and a cortical and subcortical motor network [115]. Slow reaction times, on the other hand, were associated with greater activation within midline brain structures involved in the default brain mode (see above), which the authors hypothesised to underlie inattention and task disengagement [115]. These findings may start to provide a neuroanatomical basis for the state instability hypothesis.

The state instability hypothesis could be derived and tested by means of the PVT. Indeed, it seems that this is the only test known so far to provide all the prerequisites to accurately measure both circadian rhythms in performance and the effects of sleep deprivation.

5. Neuroanatomical approach

The 'wake state instability' hypothesis allows the development of a heuristic approach to investigate cognitive functioning in chronobiological and sleep research. It takes earlier findings into consideration and integrates theoretical frameworks as the lapse hypothesis and the two-process model. However, its empirical significance is limited to one performance feature only, vigilance. Furthermore, it discounts the underlying processes leading to the performance variations. They might be consequences of physiologic changes (such as temperature), as the arousal theory of time of day effects suggests. Alternatively, it might be a matter of mediating processes, such as endocrine changes following sleep loss, which interfere with optimal cognitive functioning [118]. Another possibility is that performance behaviour is a co-equal output system, as are sleep and circadian modulated systems (i.e. melatonin secretion). Recent findings at the anatomical level of the brain support the latter concept. The sleep-active ventrolateral preoptic nucleus (VLPO) of the hypothalamus and the wakefulness-maintaining posterior lateral hypothalamus seem to provide a robust flip-flop switch for sleep–wake control [74]. The SCN projects indirectly via the dorsomedial hypothalamus (DMH) to the VLPO [74] and to major arousal-promoting cell groups [119]. Recently, wake-active dopaminergic (DA) neurons in the ventral periaqueductal gray matter (vPAG) have been identified and can be added as a new component to the above mentioned flip-flop switch [120]. As such, they constitute the decisive functional link between the homeostatic and circadian systems on the one hand and the behavioural arousal system on the other: two arousal systems can be differentiated, an internally driven, slowly adapting arousal state associated with DA and acetylcholine, in contrast to the externally stimulated cortical arousal system which rapidly adapts to transient changes and is modulated by noradrenergic (NA) neurotransmission [121]. Both these systems become manifest in output of vigilance performance such as assessed in the PVT. It is well-known that the locus coeruleus (LC) influences the activity of a variety of central nervous system functions related to alertness, vigilance and attention and also related to thalamocortical oscillations which modulate the throughput of sensory input to the cortex [122]. The above-mentioned anatomical circuit of SCN, DMH, and arousal-promoting cell groups including the LC had been proposed to be the basis for the circadian regulation of LC activity [77]. Thus, LC noradrenergic neurons might mediate the circadian and homeostatic dependent activation to the noradrenergic, rapidly adapting, thalamocortical arousal system, whereas the circadian modulated and sleep dependent rhythmicity of the internally driven dopaminergic and cholinergic energetic state might be mediated by the vPAG dopaminergic neurons, sharing projections with the VTA dopaminergic cells to the prefrontal cortex [123].

6. Conclusion

Waking neurobehavioural performance 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 neurobehavioural decrements, which can become cumulative. This has been best demonstrated by the PVT. As for the PVT, standard procedures are needed for tasks pinpointed higher cortical functions (e.g. planning, logical reasoning, etc.) along with more information about time-dependent changes in the neural basis of task performance. There is little theoretical framework but only a few descriptive hypotheses on mechanisms underlying performance decrements in this field. The wake state instability hypothesis emphasises the variability of performance as the main feature reflecting sleep homeostasis and circadian modulation, which have been evidenced by means of the PVT. Sleep-related and circadian modulated attentional deficits are assumed to be causative for decrements also in higher cognitive functions [124]. Astonishingly, this explanation, which is obvious from the neuropsychologic point of view, has been ignored for the last 15 years. Instead, all kinds of originally clinical tasks had been employed and related to circumscribed brain regions in order to develop a broad profile of cognitive impairments.

Especially prefrontal cortex-related functions show significant impairments after sleep deprivation. It remains to be elucidated whether these impairments are caused by the sleep/wake and circadian dependent modulated vigilance level, which is the prerequisite for intact cognitive functioning, or whether

higher cognitive functions are also directly modulated by the respective hypothalamic structures. The latter possibility does not seem unreasonable in the light of the recently discovered wake-active dopaminergic neurons in the vPAG with their efferent projections to the prefrontal cortex, an area being particularly innervated by dopaminergic neurons. However, to dissociate vigilance from higher cognitive functions in order to assess the effect level of the hypothalamic influence on cognition is equal to cutting the Gordian knot. Together with the methodological constraints, this promises a fascinating challenge for future research on sleep–wake and circadian related influences on different cognitive domains. The implications may be most significant for the acquisition and improvement of skills, and for the prevention of impaired performance and errors in people who work at night out of phase with their internal circadian physiology.

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