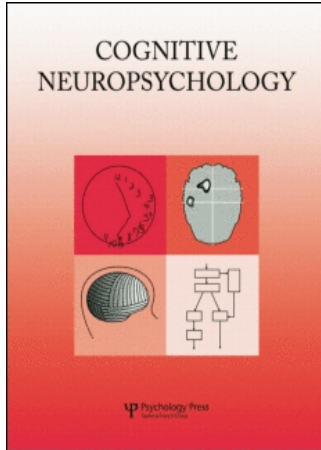


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A time to think: Circadian rhythms in human cognition

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A time to think: Circadian rhythms in human cognition

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Although peaks and troughs in cognitive performance characterize our daily functioning, time-of-day fluctuations remain marginally considered in the domain of cognitive psychology and neuropsychology. Here, we attempt to summarize studies looking at the effects of sleep pressure, circadian variations, and chronotype on cognitive functioning in healthy subjects. The picture that emerges from this assessment is that beyond physiological variables, time-of-day modulations affect performance on a wide range of cognitive tasks measuring attentional capacities, executive functioning, and memory. These performance fluctuations are also contingent upon the chronotype, which reflects interindividual differences in circadian preference, and particularly upon the synchronicity between the individuals' peak periods of circadian arousal and the time of the day at which testing occurs. In themselves, these conclusions should direct both the clinician's and the researcher's attention towards the utmost importance to account for time-of-day parameters when assessing cognitive performance in patients and healthy volunteers.

Keywords: Time of day; Circadian; Chronotype; Cognitive performance; Ageing.

INTRODUCTION

Temporal fluctuations in neurophysiological parameters are driven by two interacting processes: the homeostatic sleep pressure, which increases with time spent awake, and the circadian

pacemaker, which drives a nearly 24-hr endogenous oscillatory process (Rogers, Dorrian, & Dinges, 2003). There is evidence that the interaction between homeostatic and circadian factors is not linear throughout the day and can affect a wide range of neurobehavioural events. However, the

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impact of potential time-of-day variations on brain activity and cognitive performance remains largely ignored in cognitive psychology and neuropsychology, despite the fact that Ebbinghaus (1885/1964) already reported more than one century ago that learning of nonsense syllables is better in the morning than in the evening. One possible explanation for this apparent lack of interest is that most studies in the circadian domain have focused on the impact of time of day on vigilance and basic attentional parameters. Therefore, it remains to ascertain whether, and to what extent, higher order cognitive and intellectual abilities are modulated by the time of day and whether they show different diurnal fluctuations from vigilance parameters. Such information may have important consequences in evaluating cognitive and neuropsychological functions in clinical and experimental settings. Indeed, if performance on a given task is proven to be particularly sensitive to time-of-day effects, then there is a risk to draw substantially different conclusions depending on whether the time of testing was favourable or unfavourable for performance at this specific task. Furthermore, this confounding effect can be particularly prominent in studies involving elderly subjects, especially when attempting comparisons with young adults, because it has been shown that the process of ageing significantly affects circadian and sleep variables (e.g., Hofman & Swaab, 2006; Monk, 2005; Munch et al., 2005).

In the present review, we aim at attracting the reader's attention towards the role of the homeostatic and circadian processes in the modulation of cognitive functioning in humans. First, we introduce the basics of circadian- and sleep-dependent mechanisms underlying time-of-day fluctuations of performance. Next, we present the advantages and limitations of the main techniques that have been developed to explore these temporal fluctuations. We then provide an overview of those studies having investigated the relationships between cyclic diurnal variations and cognitive or neurobehavioural functioning. This section is divided by cognitive domains. Studies having explicitly investigated time-of-day modulations in the elderly are

reviewed in a separate section. Finally, the contributions from these various studies and their potential implications are summarized and discussed with regard to current cognitive and neuropsychological concepts.

MECHANISMS UNDERLYING THE REGULATION OF THE SLEEP-WAKE CYCLE

The circadian and homeostatic regulation of sleep

The sleep-wake cycle is regulated by two mechanisms acting either in synchrony or in opposition to each other along the 24-hr cycle: the homeostatic process and the circadian timing process. These two mechanisms have been conceptualized in the two-process model of sleep-wake regulation initially proposed by Borbély and colleagues (Borbély, 1982; Daan, Beersma, & Borbély, 1984; see Figure 1). This model, originally developed to predict sleep regulation, has increasingly been applied to estimate human neurobehavioural performance, which is also modulated by these two processes. On the one hand, the homeostatic process S (see Appendix A for a list of abbreviations used in this manuscript) is defined as a homeostatic sleep-promoting process, which continuously accumulates during time spent awake. Process S is concomitant with a decrease in waking cognitive performance and alertness and an increase in sleepiness/fatigue. During sleep, particularly non-REM (rapid eye movement) or slow-wave sleep, process S continuously decreases (i.e., sleep pressure dissipates). On the other hand, the circadian timing process C (also known as the circadian pacemaker) is best described as a nearly 24-hr endogenous oscillatory variation for sleep propensity. Circadian-based sleep propensity is at its lowest level during the early evening hours, when homeostatic sleep pressure is high, and reaches its maxima during the early morning, when homeostatic sleep pressure is low (Van Dongen & Dinges, 2003). Process C is a clock-like process, independent of whether the person is asleep or awake, which is synchronized

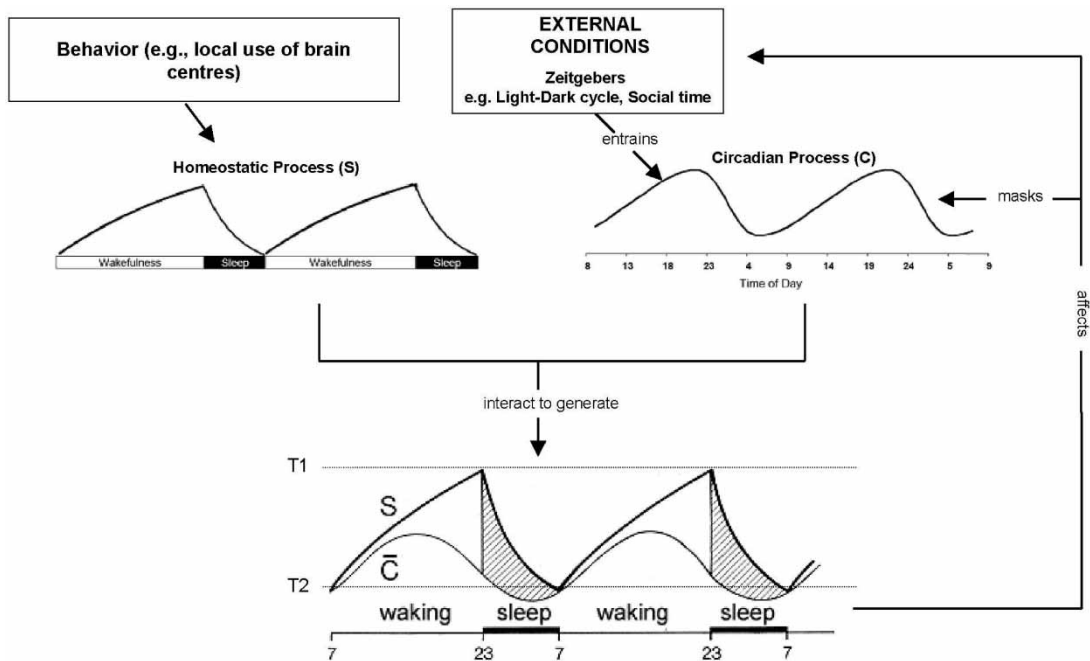


Figure 1. Representation of the two-process model of sleep regulation modified from Borbély (1982) and from Daan, Beersma, and Borbély (1984). Sleep propensity, reflected by the homeostatic process S , builds up during wakefulness and declines during sleep. The two thresholds ($T1$ and $T2$) delimiting S are modulated by a circadian process (C). A circadian pacemaker entrained by external Zeitgebers generates or synchronizes various physiological circadian oscillations. The masking effect in this context is considered as the overruling by external factors of the expression of the endogenous rhythm. It can be seen in contrast to the entrainment, defined as the coupling of an endogenous rhythm to a Zeitgeber with the result that both oscillations have the same frequency. Behaviour or more specifically the local use of brain centres as induced, for example, by a learning task might have an impact on the local sleep homeostatic drive (e.g., Huber, Ghilardi, Massimini, & Tononi, 2004). External circumstances also affect the final output of these two processes in order to define our specific sleep-wake behaviour.

with external time in normal conditions. In humans, the phase of the endogenous circadian pacemaker (process C) can be indirectly inferred by measurements of the endogenous core body temperature (CBT) rhythm or the endogenous pineal melatonin secretion. For instance, endogenous melatonin secretion reaches its nadir at the time of minimal circadian sleep propensity and its maxima at the time of maximal circadian sleep propensity. CBT actually shows the opposite pattern. Furthermore, process C is controlled by the suprachiasmatic nuclei (SCN) located in the anterior hypothalamus. This anatomical structure supports numerous periodic biological functions and is considered as the circadian master clock in most living organisms.

At any given time, the magnitude of sleepiness, alertness, and fatigue is determined by the

interacting influences of C and S . For instance, after homeostatic sleep pressure has mostly dissipated over the first 3–4 hours of the night, it is the high circadian-based propensity for sleep that prevents us from waking up in the early morning hours. Conversely, it is the very low circadian-based propensity for sleep that prevents us falling asleep early in the evening hours when homeostatic sleep pressure is at its highest level. In both cases, C and S systems work in opposition to ideally ensure a consolidated period of sleep or wakefulness. At variance, we fall asleep when the circadian propensity for sleep is coincident with a high level of sleep pressure after several hours of wakefulness, and we wake up when both sleep pressure and sleep propensity are low—that is, when the C and S systems work in synchrony. It should be noticed that since the

period of the circadian process is not exactly 24 hours, it must be resynchronized by periodic factors from the environment. In humans, the major “Zeitgeber” (i.e., time giver or synchronizer) playing this role is the periodically occurring light–dark cycle.

From a cognitive perspective, the two-process model of sleep–wake regulation entails that neurobehavioural efficiency may change over the day because of increasing homeostatic sleep pressure, because of the fact that the circadian timing system supports more or less optimal performance efficiency to the task, or because of a combination of these influences (Carrier & Monk, 2000). Importantly, stable levels of vigilance can be maintained during daytime when the circadian timing system opposes the wake-dependent (or homeostatic) arousal deterioration (for a review see Cajochen, Blatter, & Wallach, 2004a). As shown in the next section, however, large interindividual differences can be observed in the temporal disposition of an individual, giving rise to differential time-of-day fluctuations.

Interindividual differences in circadian parameters and ageing

The existence of prominent interindividual variations in the circadian timing system markedly impacts on the daily temporal organization of a large scale of human behaviours. Morningness–eveningness is the most substantial source of this interindividual variation such as “... *extreme “larks” wake up when extreme “owls” fall asleep*” (p. 80, Roenneberg, Wirz-Justice, & Mellow, 2003). Differences in the timing preference are expressed over favourite periods of diurnal activities, like working hours, and in specific sleep habits (Taillard, Philip, Coste, Sagaspe, & Bioulac, 2003) that reflect the particular chronotype of an individual. At one end of the continuum the extreme morning types (i.e., the “larks”) are located who show a marked preference for waking up at very early hours and find it difficult to remain awake beyond their usual bedtime. 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 have extreme difficulties in getting up in the morning.

The morningness–eveningness chronotype can be evaluated using self-report questionnaires, the most popular being the Morningness–Eveningness Questionnaire (MEQ; Horne & Östberg, 1976) and the Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003). High and low scores on these scales identify morning-type and evening-type individuals, respectively, whereas intermediate scores refer to neutral types. Indeed, the timing of self-selected sleep is multifactorial. It includes, beside genetic dispositions, sleep debt accumulated on workdays, work schedules in themselves, social factors influencing decisions about when to go to bed, meal timing, and light exposure (the “Zeitgebers” mentioned earlier). Neutral types are predominantly synchronized and adapted to external environmental conditions such as light–dark cycles or social obligations. At variance, it is proposed that extreme chronotypes are “phase shifted” according to their circadian rhythmicity—that is, their peaks and troughs of physiological circadian markers (CBT, melatonin) occur earlier (phase advance, morning types) or later (phase delay, evening types) in relation to the external clock time than do those of neutral chronotypes (Baehr, Revelle, & Eastman, 2000; Bailey & Heitkemper, 2001; Duffy, Rimmer, & Czeisler, 2001). Most importantly, in addition to differences in physiological parameters, the diurnal profile of some neurobehavioural variables is also chronotype dependent such that performance peaks have been observed at different clock times according to the specific chronotype of an individual (e.g., Bodenhausen, 1990; Hasher, Chung, May, & Foong, 2002; Hasher, Zacks, & Rahhal, 1999; Horne, Brass, & Pettitt, 1980; Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1998; May, 1999; May, & Hasher, 1998; May, Hasher, & Stoltzfus, 1993; West, Murphy, Armilino, Craik, & Stuss, 2002). Hence, peaks and troughs in alertness are partially contingent upon the individual chronotype expressed through preferences in the timing of daily activities, such as some people are consistently at their best in the morning whereas others are more alert and perform better in the evening. Those peaks and troughs can be partially retrained

by the action of diverse “Zeitgebers”. Light impulses at specific times of the day, for example, may help to attenuate phase delays and advances in extreme evening and morning types, allowing the individual’s circadian rhythmicity to be synchronized to external needs like work availability or social obligations. Furthermore, it is worth mentioning here that the absence of a clear morningness or eveningness preference does not mean an absence of peaks and troughs in circadian rhythmicity. Indeed, this preference is superimposed to the general circadian pattern of sleep propensity, which parallels the CBT curve over the 24-hr day, all chronotypes being confounded. Additionally, an important factor to account for in circadian studies is that the process of ageing interacts with the morningness–eveningness dimension described above. Indeed, morning types represent the majority of elderly people (75%) whereas they are only a minority in young adults (7% only; Yoon, May, & Hasher 1999), which is in line with the earlier schedule of their preferred wake times (e.g., Monk, 1997; Monk, Kupfer, Frank, & Ritenour, 1991). Objective measurements of physiological parameters confirmed this trend toward morningness by showing that the phase of the circadian timing system occurs earlier in older than in young adults (Duffy, Dijk, Klerman, & Czeisler, 1998). This shift toward morningness appears to begin around age 50 and occurs cross-culturally (Adan & Almirall, 1990; Ishihara, Miyake, Miyasita, & Miyata, 1991; May, 1999; May & Hasher, 1998; May et al., 1993; Mecacci, Zani, Rocchetti, & Luciola, 1986; Wilson, 1990; Yoon et al., 1999). However, this advanced sleep phase cannot be completely explained by a general advance of the circadian timing system with age since normal circadian rhythms have been observed in physiological parameters like CBT rhythms. It suggests that the age-related shift towards morningness could rather reflect a weaker transduction of the circadian signal downstream from the circadian timing system (Monk & Kupfer, 2000; but see Münch et al., 2005).

These modifications are important with regard to the assessment of cognitive ageing, as studies have revealed that whereas performance of younger adults often improves over the day, it

deteriorates in older adults (mainly in the executive function domain, but also in memory tasks), indicating that optimal performance is achieved when subjects are tested at the preferred time in their respective chronotype (Hasher et al., 1999; Yoon et al., 1999). Consequently, age-related differences are more likely to be disclosed when older adults are tested at their nonoptimal time of the day (e.g., Intons-Peterson, Rocchi, West, McLellan, & Hackney, 1999; May et al., 1993).

EXPLORATION PARADIGMS

In this section, we are discussing key study paradigms that have been used to explore circadian and homeostatic contributions to time-of-day modulation in neurophysiological and cognitive parameters: forced desynchrony, constant routine, and chronotype-based paradigms.

The forced desynchrony paradigm

Under normal, so-called *entrained* conditions, the sleep–wake cycle and the circadian rhythms of various physiological and cognitive functions are synchronized with each other and with the diurnal light–dark cycle. In humans, the timing of sleep and wakefulness is such that the main sleep episode 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. This synchronism makes it impossible to disentangle the respective contributions of the circadian and homeostatic processes under entrained conditions.

During a forced desynchrony (FD) protocol, subjects are isolated from the usual time givers (i.e., Zeitgebers) and are exposed for weeks to an artificial sleep/wake schedule with a “day” duration that is significantly shorter (e.g., 19 hr) or longer (e.g., 28 hr) than the normal 24-hr day. As “days” are passing by, the procedure forces a progressive desynchronization of the artificial sleep–wake cycle from the endogenous circadian cycle. Indeed, the endogenous circadian pacemaker becomes unable to keep track of the imposed, extreme sleep–wake cycle and consequently starts to follow its own rhythm. In other

words, it starts “free running” (Kleitman, 1987; see Figure 2). This paradigm has the unique advantage to truly separate the influence of homeostatic sleep pressure from that of the circadian pacemaker. However, the disadvantage of the FD protocol is that the technique is extremely time consuming and difficult, since subjects have to be kept for weeks in a room strictly isolated from the usual external circadian synchronizers (i.e., the Zeitgebers) such as daily light and temperature variations, but also from culturally and socially related cues (for instance, meal times or sounds typically associated with the beginning or the end of a day’s work).

The constant routine paradigm

Constant routine (CR) protocols have been applied to unmask endogenous circadian rhythms (Czeisler, Ronda, & Kronauer, 1985; Mills, Minors, & Waterhouse, 1978) normally embedded within the

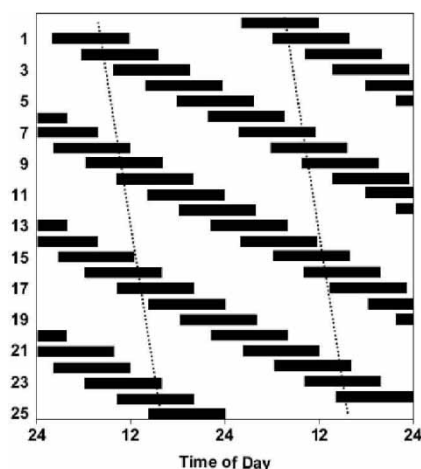


Figure 2. Triple-raster plot of a 25-day forced desynchrony protocol. In this example the subjects were placed on a 28-hr rest–activity cycle and light–dark cycle during which the subjects were scheduled to be awake for 18.7 hr and asleep for 9.3 hr. The black bars indicate the distribution of scheduled 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. The data are plotted with respect to clock time. Note. From “Circadian and Sleep–Wake Dependent Impact on Neurobehavioural Function”, by C. Cajochen, K. Blatter, and D. Wallach, 2004, *Psychologica Belgica*, 44, p. 62. Copyright 2000 by the Belgian Society of Psychology. Reprinted with permission.

sleep–wake cycle. Indeed, any external (e.g., body posture, food, light) or internal (stress level, digestion, motivation) factor has the potential to mask the “true” endogenous rhythm in modifying physiological or behavioural responses. Therefore, disclosing genuine rhythmic clock outputs, whether physiologic or behavioural in nature, requires a strong control over all possible exogenous or endogenous cues in order to avoid their masking influence on the measured variables. Thus, subjects engaged in a CR protocol have to stay awake for more than 24 hours in an isolated environment under constant conditions—that is, constant levels of ambient light and temperature, constant body posture position (semirecumbent posture in bed), and constant food intake (hourly isocaloric snacks). Physiological and behavioural measurements are normally assessed at fixed equidistant time intervals. By keeping all rhythmic external masking factors such as posture changes, light level, food intake, or physical activity highly controlled and at a minimum, the CR protocol thus allows one to quantify endogenous phase or amplitude of the hands of the clock (overt rhythms like CBT and melatonin). Furthermore, it is possible to measure the influence of the circadian system and the sleep/wake homeostat on cognitive performance. A limitation of the CR protocol is that there is no desynchronization between the sleep–wake cycle and the circadian pacemaker, which therefore does not allow a segregation of these two processes. Nonetheless, it remains possible to investigate to some extent the contribution of sleep pressure, by comparing one condition in which subjects are totally sleep deprived during the entire experiment (high sleep pressure) to another condition in which they are allowed to nap regularly, the latter keeping homeostatic sleep pressure at a low level.

Chronotype-based investigation under normal day–night conditions

Several studies have examined the temporal fluctuations of performance over the normal working day while considering the individual’s circadian preference—that is, the chronotype as

independent measure. In these protocols, performance tests are administered at optimal or nonoptimal time of day, as inferred for each subject by the score obtained at morningness–eveningness questionnaires (Horne & Östberg, 1976; Roenneberg et al., 2003). Usually, the underlying hypothesis is that subjects tested at their optimal time of day will be more efficient than subjects tested at their nonoptimal time of day, an effect referred to as the “synchrony effect” (May & Hasher, 1998). Initial studies based on the synchrony effect aimed at documenting performance decrements from optimal to nonoptimal times of day (Hasher, Goldstein, & May, 2005), especially in older adults who are rather morning types compared to younger adults who are rather evening types, tested either first in the morning (8 or 9 – a.m.) or first in the afternoon (4 or 5 p.m.). This approach, which targets interindividual differences in circadian preference, has the advantage to be relatively easy to implement than the above FD or CR paradigms. However, it also markedly suffers from the fact that it does not take the interplay between clock- and sleep-dependent processes into account (sleep pressure, circadian sleep propensity, sleep inertia, etc.) and therefore makes it impossible to segregate the respective contributions of the homeostatic S and circadian C processes to performance.

Which paradigm for what?

As described above and illustrated in Figure 3, FD, CR, and chronotype-based paradigms differ considerably in the way they control for circadian and homeostatic parameters. Therefore, cyclic variations in cognitive performance have to be cautiously interpreted in the framework of the paradigm used. From a cognitive neuropsychological perspective, it must be noticed that a major difficulty that arises when using CR and FD protocols is the design of cognitive tasks that can be administered at regular intervals, without confounding influences of circadian and homeostatic factors with the practice effect on the task (e.g., testing of executive functions that requires a novelty component), or with the contribution of embedded

learning and memory components. In chronotype-based approaches, the task is either administered only once in separate cohorts, or repeated at two times of the day in parallel versions in a within-subject design. In this respect, and despite its intrinsic limitations, the chronotype-based paradigm might be more appropriate for studying the influence of the biological clock on performance variations in high-order cognitive functions as a function of time of day than is a CR or a FD paradigm.

TIME-OF-DAY MODULATIONS IN COGNITIVE PERFORMANCE

When looking at cyclic variations in cognitive performance, it must be noticed that many cognitive aspects are confounded in the literature dealing with circadian and homeostatic modulations in subjective and objective performance measures. It is therefore necessary to clarify the definition of some terms in the following. We refer in the remaining of this paper to *subjective alertness* as the mere subjective experience of feeling alert. For example, this can be subjectively investigated using visual analogue scales. Likewise, *subjective sleepiness* refers to the experience of feeling a need for sleep, which can be assessed using self-report scales (e.g., from “not asleep at all” to “to the verges of falling asleep”). Note that alertness and sleepiness should not necessarily be assumed to be reciprocal states, since studies indicated that subjective states of impaired alertness and excessive sleepiness are independent constructs in the evaluation of sleep-disordered patients (e.g., Moller, Devins, Shen, & Shapiro, 2006). Finally, the cognitive functioning domains, ranging from simple attention to logical reasoning, working memory, long-term memory, and complex executive functions, are usually assessed through objective *performance* measures via specific tasks. A summary view of the main cognitive processes surveyed in the present report and their mutual organization is illustrated in Figure 4.

In the following, we first review the issue of subjective measures of alertness and sleepiness and then

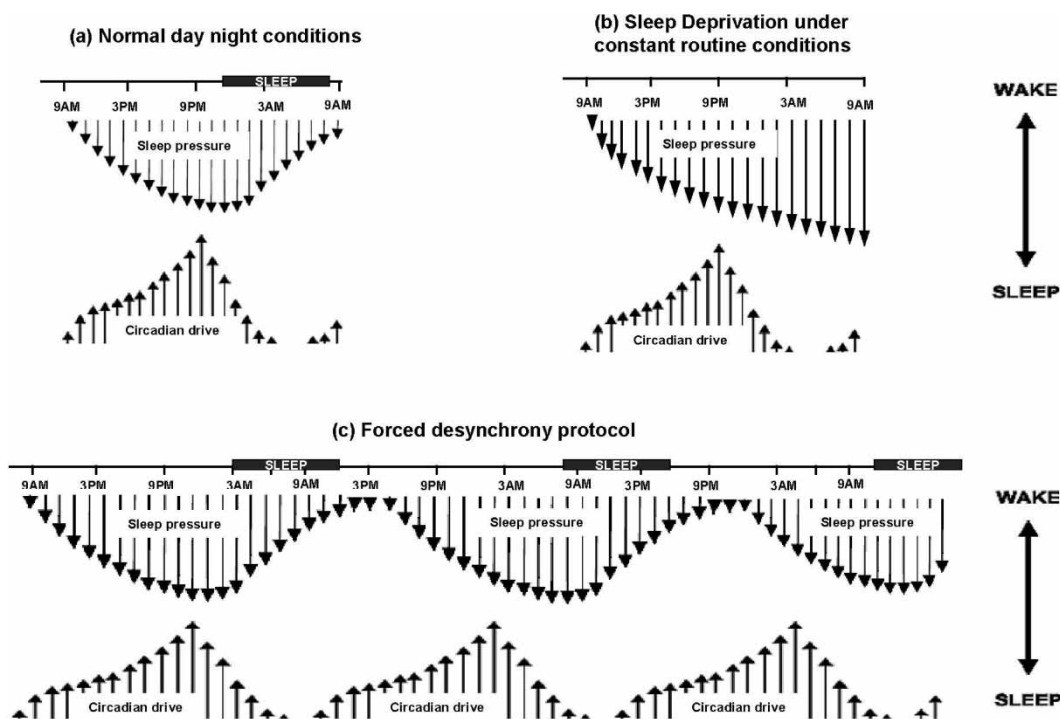


Figure 3. Schematic representation of the interaction of sleep pressure (homeostatic pressure) and the circadian drive during (a) normal day–night conditions, (b) during sleep deprivation under constant routine conditions, and (c) during a forced desynchrony protocol. During the normal day–night condition protocol, the independent variable is most frequently the individual’s circadian preference (chronotype); the sleep episode and the two processes are in this way scheduled to differential times of the day according to the individual’s preferred sleep–wake schedule. In the present figure a neutral chronotype is reflected with habitual sleep time of 11 pm. During the constant routine protocol, the sleep pressure is manipulated (steady increase) allowing an observation of the circadian alerting signal under different sleep pressure conditions. The forced desynchrony paradigm allows the observation of scheduled episodes of sleep and wakefulness at virtually all circadian phases. Modified from Edgar, Dement, & Fuller (1993).

outline time-of-day influences on more complex and cognitive performance measures such as attention, memory, and executive functions. The questions that are addressed here are: are there consistent, genuine associations between circadian patterns in physiological parameters and subjective or objective performance measures, and do they differ based on the cognitive domain explored? If not, we further question whether these discrepancies can be explained by differences in experimental designs including the use of more or less controlled exploration paradigms. Each section is concluded by a synthesis of the main evidences yielded so far for the hypothesis that time-of-day fluctuations play a role in performance measures of cognitive functioning.

However, first we provide a short historical background on the relationships between cognitive processes and time-of-day variations.

Historical background

The interest in cyclic performance fluctuations is not novel. Very early studies mainly focused on the determination of the most favourable time of day for teaching in order to optimize school timetables (e.g., Gates, 1916; Laird, 1925). Kleitman (Kleitman, Titelbaum, & Feiveson, 1938), who is generally credited for having first established a systematic link between cognitive performance, chronobiology, and sleep, evidenced later on a

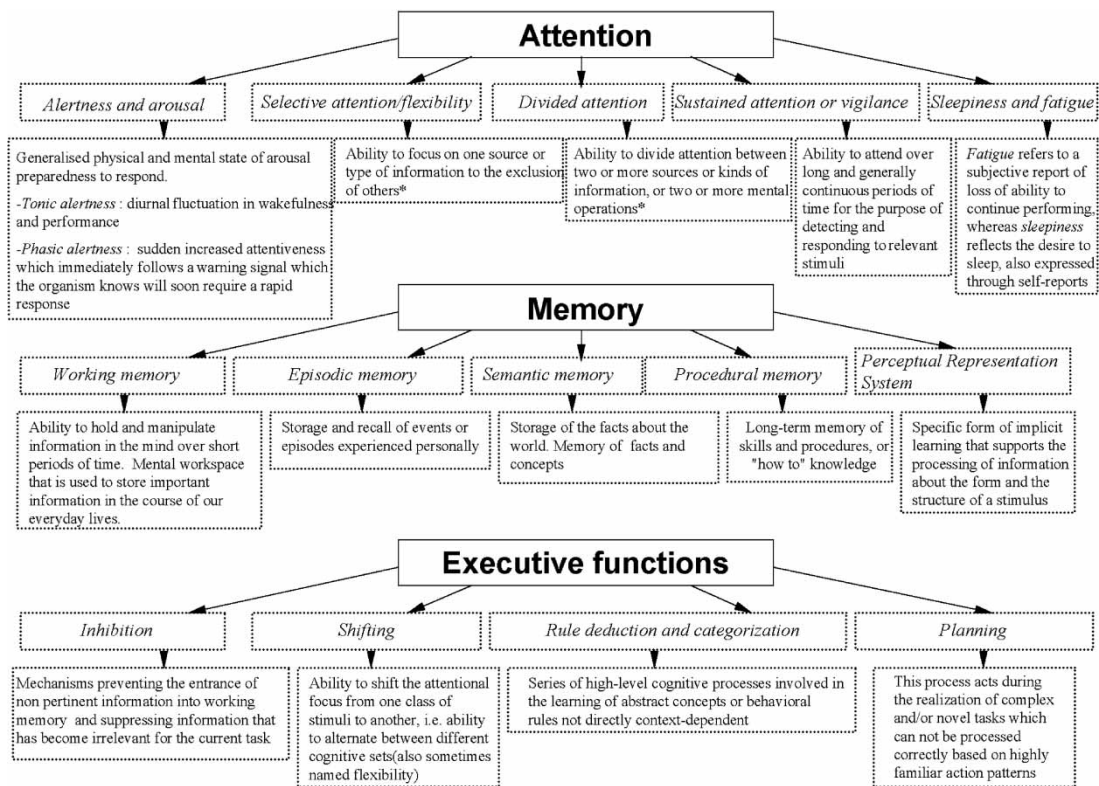


Figure 4. Overview and global classification of the main cognitive processes. *This process is also classified into executive functions.

parallelism between the circadian rhythm of core body temperature (CBT) and time-of-day effects in performance for simple repetitive tasks (e.g., card sorting, mirror drawing, copying, and code substitution), a finding later replicated by Colquhoun (1981). This and many other studies disclosed a temporal relationship between circadian variations in cognitive performance measures and daily fluctuations in physiological variables, such as when CBT is high, neurobehavioural performance levels also tend to be high, whereas low CBT or high endogenous melatonin secretion are associated with reduced levels of neurobehavioural performance and alertness. Kleitman et al. (1938) explained this association by arguing that accuracy and speed in performance are contingent upon levels of muscle tonicity and in turn on the metabolic activity of the cells of the cerebral cortex. He therefore surmised that raising the

latter through the circadian-related increase in body temperature would indirectly speed up cognitive processing. Finally, Aschoff and Wever (1976; Wever, 1979) demonstrated in a FD protocol that diurnal performance rhythms are clearly related to the circadian system in humans, by quantifying for the first time the period of the "circadian performance rhythm" to 24.8 hr.

However, a wider range of subsequent studies disclosed the influence of other, unrelated parameters on time-of-day effects in revealing the existence of different peaks and troughs of performance throughout the day, which are actually contingent upon the type or difficulty of the task (e.g., differential working-memory load; Folkard, Wever, & Wildgruber, 1983). While performance speed on simple repetitive (Colquhoun, 1981) and serial search tasks (Monk, 1982) peaks with temperature levels in the evening, speed performance on more

complex cognitive tasks (e.g., logical reasoning tasks; Folkard, 1975) peaks in the late morning, and performance in short-term memory retention peaks in the early to mid-morning (e.g., Laird, 1925). These findings led to the hypothesis that the time of day at which a cognitive test is optimally completed is largely dependent on the specific parameters of the task, including the cognitive domain it belongs to, its duration and difficulty, the administration method, and the measured variable (Bonnet, 2000). Further studies indicated, however, that drawing conclusions at this stage relies critically on the paradigm used. For instance, although a linear decline in short-term memory over the waking day was present under a nycthemeral schedule (sleep at night and wakefulness during daytime), a parallelism between variations in performance and in body temperature levels re-emerged when testing was extended into an unmasking constant routine (CR) protocol with 40 hr of continuous wakefulness (e.g., Cajochen, Khalsa, Wyatt, Czeisler, & Dijk, 1999), casting doubt upon the presence of a general inversion of short-term memory and body temperature rhythms.

Additionally, it was pointed out that appropriate conclusions regarding changes in performance can be drawn only after controlling for the influence of a series of primary factors such as motivation (Hayashi & Hori, 1998; Mavjee & Horne, 1994; Minors & Waterhouse, 1983), stress (Orr, Hoffman, & Hegge, 1976), food intake (Paz & Berry, 1997), posture (Krauchi, Cajochen, & Wirz-Justice, 1997), ambient temperature (Mavjee & Horne, 1994), caffeine consumption (Ryan, Hatfield, & Hofstetter, 2002), physical activity (Bugg, DeLosh, & Clegg, 2006), or lighting conditions (Leproult, Van Reeth, Byrne, Sturis, & Van Cauter, 1997), all parameters that can exert a masking influence on the circadian profile of neurobehavioural functions. These studies have demonstrated that cognitive performance is not solely determined by the underlying regulatory activation system, but also modulated by compensatory mechanisms, such as motivational factors or expectancy due to experience. In this respect, observed propensity for sleepiness in the early afternoon contrasting with the circadian

peak of alertness in the early evening has been explained by "interest" or motivational aspects (e.g., Mavjee & Horne, 1994). Due to such mechanisms, circadian modulation in cognitive performance can be masked and even levelled off under some circumstances, since these mechanisms are able to briefly compensate for circadian fluctuations—for instance, levels in wakefulness (e.g., Kraemer et al., 2000).

Time-of-day fluctuations in subjective alertness and sleepiness

Sleepiness and alertness states are in the background of most cognitive processes, even if not systematically modulating performance. Circadian rhythmicity for such subjective self-report measures is usually assessed by visual analogue scales (VAS; Monk, 1989), Likert-type rating scales such as the Karolinska Sleepiness Scale (KSS; Akerstedt & Gillberg, 1990), and the Stanford Sleepiness Scale (SSS; Hoddes, Dement, & Zarcone, 1972).

The circadian rhythm of subjective alertness is not a simple reflection of an "arousal rhythm" parallel to the CBT rhythm. Although the circadian-driven temperature oscillator is certainly one determinant of subjective alertness, it is also influenced by the homeostatic process controlling the sleep-wake cycle. This is further corroborated by the fact that we decide to go to bed when our sleep pressure or sleepiness level has achieved a certain accumulation level (Monk, 1987). In a 72-hr sleep deprivation protocol, Froberg (1977) observed a clear circadian rhythm in both subjective alertness and CBT. These two rhythms were parallel, showing identical times of peak and trough and a statistically reliable correlation, suggesting that the endogenous circadian oscillator responsible for the body temperature rhythm is a major determinant of subjective alertness, at least under conditions of 72 hr of continuous wakefulness under temporal isolation. More recent results have been remarkably consistent in indicating that subjective alertness varies in parallel with objective vigilance measures, with detectable declining around the usual bedtime (e.g., Carrier & Monk, 2000; Dijk, Duffy, & Czeisler, 1992; Johnson et al., 1992; Monk, Buysse, Reynolds,

Kupfer, & Houck, 1996). This decrease in subjective alertness continues until a minimum is attained in the early morning hours, 1 to 2 hours after the minimum of body temperature—that is, between 6 and 8 a.m. in most young adults (Dijk et al., 1992; Gillberg, Kecklund, & Akerstedt, 1994; Leproult et al., 1997). Subjective alertness then increases, despite sustained wakefulness, suggesting that activating mechanisms become operative in the morning.

The similarity of the temporal pattern of alterations in subjective and objective alertness during extended wakefulness has led to the assumption that their respective degrees of impairment are quantitatively correlated, suggesting that individuals who feel subjectively more sleepy are also more cognitively impaired (in Leproult et al., 2003). The current literature, however, does not completely confirm this intuitive assumption. There is accumulating evidence that subjective sleepiness and objective alertness are not necessarily related to performance measures during sleep deprivation protocols (Frey, Badia, & Wright, 2004; Leproult et al., 2003). Furthermore, under conditions of chronic sleep deprivation, subjective measures of alertness and neurobehavioural performance can differ substantially (Van Dongen, Vitellaro, & Dinges, 2005). Prior cognitive activity also influences subjective estimates of sleepiness and can interact with circadian effects if not properly controlled when measuring rhythmicity in subjective states (Babkoff, Caspy, Mikulincker, 1991; Van Dongen & Dinges, 2005).

To sum up, available data suggest that the modulation of subjective alertness can be considered as the outcome of interacting circadian and homeostatic processes—the homeostatic process being differentially expressed according to the selected protocol (e.g., an increasing homeostatic pressure by a lack of sleep versus normal day–night conditions, where circadian and homeostatic are naturally “counterbalanced”). Thus, there is a need to be cautious in generalizing diurnal variations for global parameters such as “ability to perform” or “sleepiness/alertness”, which considerably depends on the way the variable is measured (Monk, 1987). Additionally, discrepancies between studies are

also partially explained by the fact that the constructs “sleepiness” and “alertness” are too often assumed to be reciprocal states of consciousness, a position that becomes more and more controversial (e.g., Moller et al., 2006). One cannot be deduced from the other, and care should be taken in future research to avoid confusion between these terms.

Time-of-day fluctuations in cognitive performance measures

Cognitive functions ranging in complexity from psychomotor vigilance to logical reasoning and complex thought have been investigated in the framework of the hypothesis of a relationship between the CBT curve and variations in performance measures. Independent of the internal biological time, direct positive relationships have indeed been observed between CBT and a variety of performance measures such as psychomotor vigilance, code substitution, and an addition task (Wright, Hull, & Czeisler, 2002), supporting Kleitman et al.’s (1938) initial postulate of a causal role for body temperature on performance. As outlined in the following subsections, however, it is unlikely that cognitive performance is directly and solely mediated by changes in body temperature. Indeed, even when correlated with subjective alertness or basic arousal measures, performance in cognitive tasks that require a certain degree of attention or vigilance level also differ in the cognitive parameters the task is challenging for. It is therefore reasonable to assume that a variety of other factors beside external and internal changes in body temperature affect the time-of-day variation in complex performance measures.

In the following sections, we review time-of-day modulations in cognitive performance measures. Starting with basic cognitive processes, we outline the contribution of psychomotor vigilance performance measures to the unification of a theoretical context and then survey circadian influences on more complex aspects of cognitive functioning. An underlying debate within these studies is whether the circadian drive equally influences all performance variables or differentially affects performance using different cognitive

domains. From a neuroanatomical perspective, the first hypothesis would imply equal circadian variations in all cerebral functions, possibly because of global metabolic changes in the brain, whereas a differential process may rely on more localized, regional variations in cerebral activity.

Attentional capacities

In the circadian domain, any discussion about attentional processes should comment first on the relationships between attention and arousal since these terms appear very closely related. It seems logical that an organism with impaired alertness would also have impaired attention. The reverse, however, is not necessarily true as normally alert individuals can exhibit attentional deficits (Gitelman, 2003). Attention results in the preferential processing of various types of cognitive information. For example, attentional enhancement can be demonstrated for objects in the environment, actions, perception of our own internal states, thoughts, space, and time (e.g., Posner, 1995). The multidimensional nature of attention has led theorists to wonder whether the concept of attention is well-conceived—that is, whether it refers to a single or clearly definable set of functions. In particular, attention has been classically divided into the global categories of phasic alertness, vigilance, selective attention, and divided attention (Sturm, Willmes, Orgass, & Hartje, 1997). The approach taken in this chapter is that although attention is not a unitary concept, it does represent a cohesive set of processes, which serve to enhance sensory, motor, and cognitive processing (see Figure 4).

There is a lack of consistency between studies having investigated the relationships between subjective alertness and objective performance measures of attention. This probably relates to the multidimensional nature of attention itself. In this perspective, it has been shown that the circadian pacemaker and the homeostatic sleep drive differentially impact on performance according to the attentional domain investigated (Horowitz, Cade, Wolfe, & Czeisler, 2003; Kraemer et al., 2000).

Vigilance and sustained attention. The ability to sustain attention during testing is a basic prerequisite for optimal performance in nearly all cognitive tests. Temporal variations in basic attentional measures have been described in numerous studies, underlining the utmost importance to understand the impact played by cyclic changes in attention on performance in higher order cognitive tasks. Appropriate investigation of attention in this context requires the use of tasks that can be easily practised and implemented into CR or FD experimental protocols, with no or minimal learning curve, and minimum intersubject variability in performance due to aptitude.

The Psychomotor Vigilance Test (PVT; Dinges & Powell, 1985), which is probably the most widely used test of sustained attention in the circadian domain, has proven to have these qualities. In this task, subjects merely have to press a button as fast as possible each time a digital counter starts, with a random interval between the onsets of the clock. Dependent measures are reaction times and response lapses.

Using the PVT, a specific temporal performance modulation of vigilance was found during CR or FD studies, such as performance initially remains fairly stable along the normal day (up to 16 hours; e.g., Cajochen et al., 1999), probably due to the circadian drive opposing the increasing build-up of sleep pressure. However, this balance subsides when the testing period extends into the biological night. From this time point, PVT performance progressively deteriorates as the duration of the wakefulness episode increases, although PVT performance is still modulated by additional reductions during the night and relative improvements during the following daytime. This demonstrates that the detrimental effect of prior wakefulness on sustained attention or vigilance is not strictly linear, but strongest close to or shortly after the minimum of the endogenous CBT rhythm, representing the peak in the circadian signal of sleep propensity (e.g., Cajochen et al., 1999; Wright et al., 2002; Wyatt, Ritz-De Cecco, Czeisler, & Dijk, 1999). In this respect, hypothesis-driven use of the PVT has substantially contributed to the evolution of a theoretical

context initially focused on a simple causal relationship between physiology and performance rhythms. Hence, it is now better conceptualized that performance variability in constant routine sleep deprivation studies is explained by modulation in basal arousal levels, due to progressive dysregulation of sleep-initiating and wake-maintaining mechanisms (see Blatter & Cajochen, 2007, for a review). At this point, it is worth questioning whether PVT profiles can be generalized to other measures of vigilance and attention and, more importantly, affects performance on other cognitive processes closer to more authentically real-life situations where we are continuously confronted to task switching, to divide our attention simultaneously on multiple goals, and so on.

PVT: Generalization to other vigilance tasks? Other vigilance tasks have disclosed similar circadian modulation profiles to the PVT (Monk, 1997), for instance the “Mackworth Clock Test” (Mackworth, 1948). This test consists in a clock-like device that provides a monotonous stimulus environment in which occasional, low, only slightly distinguishable signals are produced. The clock hand advances in discrete jumps every second on a blank background. However, at irregular intervals, averaging about every one and a half minutes, it advances a double jump that the subject must detect by pressing a key immediately.

Generalizations can also be made to simple addition/calculation tasks under time pressure (Cajochen et al., 1999; Dijk et al., 1992; Johnson et al., 1992; Wright et al., 2002; Wyatt et al., 1999). At variance, however, Lotze, Treutwein, and Roenneberg (2000) investigated daily rhythms of vigilance in 6 healthy subjects over a 24-hr period using the double pulse resolution, a visual detection task that investigates more perceptually based aspects of vigilance, and observed that optimal performance occurred around midday. This discrepant result as compared to the previous studies can be explained by different task conditions. On the one hand, PVT, Mackworth Clock, or even simple calculations represent classical measures of vigilance or sustained attention, in line with the definition proposed in Figure 4—that is, the

ability to attend over long and generally unbroken periods of time for the purpose of detecting and responding to relevant stimuli. On the other hand, the double pulse resolution task requires fine-grained temporal discrimination between two successive events separated by a few milliseconds only. Therefore, it primarily probes the efficiency of sensory systems and is probably more a psychophysical than a cognitive task in nature, although sustained attention is needed to perform the task. Furthermore, the 24-hr protocol used by Lotze et al. (2000) did not enable a complete separation between the circadian and the homeostatic components, in contrast to previous studies. Indeed, the phase relationships between the sleep–wake cycle and the temperature rhythm markedly differ between entrained (i.e., coupling of an endogenous rhythm to a Zeitgeber) and free-running conditions (Wever, 1979).

Additionally, these data already illustrate the complexity and diversity of the attentional domain since it can be argued that visual detection and simple additions are also tasks of sustained attention. The question of whether more complex attentional parameters behave similarly according to time of day is addressed in the following sections.

Selective attention. Visual search performance on a letter cancellation task can be considered as a classical testing example of *selective attention*—that is, the ability to focus on one source or type of information while excluding others. Likewise with PVT, De Gennaro, Ferrara, Curcio, and Bertini (2001) found a parallelism between the CBT rhythm and performance in various tasks of selective attention during a sleep deprivation protocol. Furthermore, this parallelism was particularly pronounced when the task had a high working-memory load (Mikulincer, Babkoff, Caspy, & Sing, 1989). Casagrande, Violani, Curcio, and Bertini (1997) also showed that a three-target letter cancellation condition is globally more sensitive than a two-letter cancellation task to vigilance variations, pointing out the role of cognitive load in the expression of time-of-day effects on performance measures. Along the same lines, Valdez et al. (2005) observed dissociations between separate attentional

components during a single cognitive task in a CR study. Significant time-of-day modulations were disclosed when looking separately at each component (tonic alertness, phasic alertness, and selective attention; see Figure 4), but this was not the case any more when all conditions were confounded in a “global vigilance” parameter, suggesting that the circadian clock does not produce equal changes in all attention-related brain functions. However, we have to notice that the only attentional measure showing no clear circadian profile—that is, the vigilance measure is not process pure since the authors quantify it as the output of the global performance level over the whole tasks, all conditions confounded. A couple of cognitive components are therefore mixed together to investigate the subject’s global concentration level rather than assessing objective vigilance.

Divided attention. In a dual-task setting, subjects need to efficiently divide attentional resources between two competing kinds of information. Van Eekelen and Kerkhof (2003) investigated rhythmic variations in divided attention during a controlled 27-hr sleep deprivation protocol. The dual-task paradigm combined a tracking pursuit task (constantly manipulating a joystick to keep the cursor on a moving target) and a self-paced memory search task (memorizing a set of four randomly selected digits, then testing in a yes/no recognition paradigm). Results revealed congruence in the daily rhythms of performance for both the single- and dual-task condition, with a linear decrease during the diurnal hours, followed by a steady increase in the morning hours peaking around 0800.

A preliminary conclusion that could be drawn from these studies is that the more complex the investigated cognitive parameter, the less abundant are the results. The scarcity of the data makes it difficult to resolve inconsistencies. Thus there is an urgent need for more and better focused studies to unravel the role of daily rhythms in multifaced aspects of attention. An additional important issue is the difficulty to repeatedly use more complex measures in the framework of CR and FD protocols and the difficulty to establish valid comparisons between studies using various tasks supposedly

tackling similar attentional functions. For instance, selective- or divided-attention parameters are too often investigated using multidetermined tasks that entail additional cognitive processes. Hence, one should take great care in the selection of a specific task if one wants to investigate time-of-day modulations on complex cognitive constructs such as attention. This precaution should enable comparisons of the different study results and ultimately allow for a generalization to real-life situations.

Memory performance

Similar to attention, memory is a generic term encompassing many specific subdomains (see Figure 4 for an illustration). Memory is primarily delineated between short-term and long-term memory stores (e.g., Ratcliff, Van Zandt, & McKoon, 1995), the former being dedicated to the temporary storage of information up to seconds, whereas information is deemed consolidated and less susceptible to disruption in the latter. Long-term memories further belong to multiple memory systems, primarily delineated between declarative (i.e., explicit) and nondeclarative (i.e., procedural or implicit) memory in men. One of the distinguishing features of declarative memory is that information encoding and retrieval is carried out explicitly—that is, the subject is aware that the stored information exists and is being accessed. Conversely, nondeclarative memories can be acquired and reexpressed implicitly—that is, although the subject is not necessarily aware that new information has been encoded or is retrieved, its behavioural performance is affected by the new memory (Peigneux, Laureys, Delbeuck, & Maquet, 2001). With the evolution of cognitive models, short-term memory has also become a component of a larger entity named working memory, whose function is both the temporary maintenance of verbal and visual information and, if necessary, its manipulation in a central executive system (Baddeley, 2003). This is why working-memory studies that are presented in the following section may also be relevant with respect to the executive function domain, which is addressed later in this review.

Working memory. Variations in working-memory tasks have been investigated relatively early in circadian studies. Working memory refers to the capacity to temporarily maintain active some information necessary for the realization of the ongoing task. In that context, researchers were rather interested in the complexity level of a task by manipulating its amount of information that must be temporarily kept active (or stored) in working memory. It was hypothesized that time course of circadian rhythms differs according to task complexity, based on the assumption that simple accuracy and speed performance measures would parallel CBT variations (and consequently basic arousal rhythms), whereas more complex measures would not parallel CBT variations and show task-specific performance peaks. In early studies mainly serial search tasks were used, which were manipulated by the number of targets to be considered. It is reasonable to consider that the challenge of working-memory load depends on the number of targets. However, the visual search task per se also challenges selective attention processes (i.e., the ability to focus on one source or type of information to the exclusion of others). Despite this fact, the study results were mainly discussed by considering the effects of manipulations of memory load on circadian rhythmicity. In this perspective, Folkard and Monk suggested that working-memory load partially determines the temporal evolution of a task over the course of the day. They showed that serial visual search performance was positively associated with the endogenous CBT rhythm when few targets were to be remembered, but not any more when the number of targets was increased (Folkard, Knauth, & Monk, 1976). The larger the short-term memory component the earlier the daytime peak in performance appeared. They proposed that this differential relationship between performance efficiency and time of day may be mediated by a qualitative and/or quantitative shift in the processes in which participants engage spontaneously, a hypothesis supported by several studies having reported that mnemonic strategies change over the day (Corbera, Grau, & Vendrell, 1993; Folkard, 1975; Folkard & Totterdell, 1994;

Folkard et al., 1983; Monk, 1982). These results suggested that working-memory component and load or mnemonic strategy parameters play an important role in the determination of the time of day at which a certain task is optimally performed, an assumption that has been confirmed in several studies (Babkoff, Mikulincer, Caspy, Kempinski, & Sing, 1988; Folkard et al., 1983; Mikulincer et al., 1989; Ramirez et al., 2006). However, unlike Folkard et al. (1983), who reported an effect of time of day dissociated from CBT variations under normal day night conditions, Monk (1997) and others (Cajochen et al., 1999; Wright et al., 2002; Wyatt et al., 1999) observed that circadian fluctuations of working-memory performance actually parallel the CBT rhythm under better controlled study conditions and when wakefulness extends into the biological night. Similarly, Van Eekelen and Kerkhof (2003) observed that the number of updates in working memory during an n-back task did not interfere with circadian rhythmicity in a controlled 27-hr sleep deprivation episode. As Folkard's studies (Folkard, 1990; Folkard et al., 1976) were performed under normal daily routine conditions, this discrepancy between studies most likely stems from the uncontrolled influence of confounding endogenous and/or exogenous factors on performance in these early experiments.

To sum up, performance on working-memory tasks seems to behave in a similar manner to that on several attentional tasks, in that intertask differences observed under normal day-night conditions may fail to appear when data collection is extended into the night and when subjects are tested at all circadian phases. One possible explanation for these similarities would be that attention is a basic component of complex working-memory tasks that affects its efficiency and subsequently performance on these tasks (Baddeley, 2003). Still, similar profiles were found in other memory domains—namely declarative episodic memory—as shown in the following section.

Declarative memory. Declarative memory encompasses two main components: episodic and semantic memory. The main distinction between these

interrelated systems is that semantic memory encompasses knowledge about the world regardless of the spatiotemporal context of acquisition whereas episodic memory refers to a system that stores events located in time and space. Diurnal rhythms in semantic memory have not been specifically investigated to the best of our knowledge. At variance, performance for episodic verbal memory tasks was examined under CR and FD conditions (Johnson et al., 1992). Immediate recall of aurally presented meaningful material (memorization of prose passages) every 2 hours indicated prominent circadian variations in memory performance. In the normal waking period, during the first 10 hours, performance steadily declined, at a time when CBT levels were gradually increasing. During the subsequent 24 hours of the CR, however, the variation in memory performance paralleled the circadian rhythms of CBT. Other CR studies using a probed recall memory task (PRM) similarly evidenced that minima of performance rhythms coincided with timing of the trough in CBT when testing was extended into the biological night, disclosing a circadian-related variation in performance (Cajochen et al., 1999; Wright et al., 2002; Wyatt et al., 1999). It is well established that episodic memory for experienced events is closely linked to strategic processes of recollection (Wagner, 1999). In this perspective, the renewed parallelism between variations in episodic memory performance, working memory, and attentional parameters may suggest that circadian variations in attention and executive strategic processes underlie variations in episodic memory performance or vice versa.

The above-mentioned studies did not take into account the individual preference in the circadian profile or controlled for it by screening for neutral types, for the most part. However, chronotype-based differences in the effects of time of day on memory have been observed during normal working-day conditions such that recall performance increased across the day for evening types but decreased for morning types, and this time-of-day effect was largest for the more difficult prose passage condition (Petros, Beckwith, & Anderson, 1990; but see Hidalgo, Zanette, Pedrotti, Souza, Nunes, & Chaves, 2004).

Procedural memory. Procedural memory mainly comprises the incidental acquisition of perceptual-motor, perceptual-verbal, and cognitive skills (e.g., Cohen & Squire, 1980) that affect behaviour without necessarily requiring conscious recollection. Cajochen et al. (2004b) have investigated circadian performance modulation on a motor sequence learning task during a 40-hr constant posture protocol under high (40 hr of sleep deprivation) and low (40 hr with interspersed naps) sleep pressure conditions. Using a serial reaction time task (SRTT; Cleeremans & McClelland, 1991), they showed that learning of sequential regularities was possible under low sleep pressure conditions only—that is, when sleep was regularly allowed. Nonetheless, increase in sleep pressure with elapsed time was not accompanied by a deterioration of global performance measures (i.e., global reaction times for random as well as learned sequences), despite higher levels of sleepiness. Most importantly, superimposed circadian modulation of performance was observed during high as well as low sleep pressure conditions, in temporal relation with the endogenous melatonin expression. Further studies are needed to determine whether such a circadian modulation in procedural learning restricts to motor sequence learning paradigms or may be generalized to other domains of nondeclarative memory—for instance, priming effects that reflect access to memories in the perceptual representation system (Tulving & Schacter, 1990).

Summing up on the memory section, available data clearly indicate that memory performance may be modulated by the time of the day at which testing occurs. Outcomes from CR and FD protocols indicate that memory performance is worse at night than during daytime, even after controlling for the confounding effects of time spent awake. However, these conclusions should be regarded with caution given the few number of studies conducted so far in this domain. Moreover, only part of the known memory systems have been investigated. Thus, it is not clear whether the sensitivity to circadian modulation is homogeneous for different memory systems. It should also be noticed that memory performance tests are not always suitable for performance assessments across multiple

sleep–wake cycles in CR or FD protocols because of significant inter- and intrasubject variability and the fact that repeated task administration adds a learning curve on performance measures (Dorrian, Rogers, & Dinges, 2005). However, data gained in chronotype-based studies, where measures are not repeated, also indicate prominent time-of-day fluctuations in memory performance. Additionally, individual preferences play an important role in such modulations. Therefore, these parameters should be more seriously taken into account while investigating memory performance in a research and clinical context.

Executive functions

Executive functions encompass a series of high-level processes, the main function being to facilitate adaptation to new or complex situations when highly practised cognitive abilities or behaviour no longer suffice (Collette, Hogge, & Salmon, 2006). Thus, they mainly serve to deal with changing environmental demands, to control the content and evolution of cognitive processes, and to maintain and protect ongoing cognitive activity against unintentional distractions. A great number of separate functions have been attributed to control (or executive) processes, such as inhibition of prevalent responses, initiation of behaviour, planning of action, hypothesis generation, cognitive flexibility, judgement and decision making, and feedback management. Executive functioning has initially been associated with activity in the frontal brain areas although an increasing number of recent studies demonstrate that different executive functions also depend upon posterior (mainly parietal) cerebral regions (e.g., Collette et al., 2006). Sleep deprivation disproportionately acts on these regions (e.g., Drummond & Brown, 2001) and affects performance at so-called “prefrontal” neuropsychological tests (flexible thinking, verbal fluency, memory for temporal order; e.g., Harrison, Horne, & Rothwell, 2000). It should be emphasized here that the assessment of executive functioning is not trivial under CR or FD conditions due to the fact that in these protocols, task repetition is a main requirement. Indeed, one of the main functions of human prefrontal cortex is to enable generation and execution of

novel goal-directed behaviour. It entails that sensible tests of executive functioning should be, by definition, novel and stimulating (Blatter, Opwis, Munch, Wirz-Justice, & Cajochen, 2005). Thus, the requirement of task novelty poses a problem since repeated testing is crucial in carefully controlled circadian studies. At each repetition of the task, the reliability and sensitivity of the executive performance measure should be questioned, and that must be taken into account when interpreting the results of these studies. Consequently, even if less controlled according to homeostatic and circadian parameters, protocols requiring fewer testing repetitions (e.g., the chronotype-based paradigm) are more appropriate for the investigation of executive functions.

Inhibition. Inhibitory mechanisms mainly prevent irrelevant information from entering working memory, thus limiting access to purely goal-directed information. This process also serves to delete or suppress information from working memory that is only marginally relevant or that was once relevant but is no longer apposite for current goals. Finally, inhibition operates to restrain strong responses from being emitted before their appropriateness can be evaluated. These functions have been investigated under various experimental conditions.

Manly, Lewis, Robertson, Watson, and Datta (2002) revealed a significant time-of-day modulation in inhibition capacities during practice of a go/no-go task. Higher accuracy in the early afternoon and evening and lower accuracy late at night and in the early morning revealed a significant time-of-day modulation in the capacity to maintain active control over a response pattern (i.e., withholding responses on unpredictable no-go trials). Conversely, the capacity to maintain response speed in highly stereotyped aspects of the task was unaffected by time of day. These results are in accordance with other studies (e.g., May et al., 1993; West et al., 2002) having shown that time-of-day modulations do not exert uniform effects on cognitive functioning and that more controlled, nonautomatic processes (that mostly rely upon prefrontal cortex activity) may be disproportionately affected by time-of-day variations. Similarly, Yoon

et al. (1999) concluded that synchrony between circadian arousal periods really matters for controlled cognitive tasks, but not for others requiring more automatic processes (e.g., vocabulary tests, simple trivial questions, familiar category judgements). They propose that alterations in cognitive functioning at off-peak times actually stem from circadian-related deficits in inhibition. In this perspective, performance at nonoptimal time of day would reflect deficits such as increased access to irrelevant information, failure to clear or suppress information that is no longer useful, and difficulties in restraining or preventing the production of strong, dominant responses that are undesirable or inappropriate. In addition, downstream consequences of diminished inhibition could include heightened susceptibility to proactive interference, impaired judgements resulting from retrieval failure, affecting by this way not only pure cognitive processes but also performance on social cognition-type tasks. Indeed, less monitoring for goal-consistent responses at nonoptimal times of day can result in more "schema driven" behaviours and increased reliance on stereotypes and heuristics. In this way, Bodenhausen (1990) observed that stereotypes act such as judgemental heuristics and are likely to be more influential under circumstances in which people are less motivated or less able to engage in more systematic and careful judgement strategies. This is in line with the hypothesis that alterations in cognitive functioning at off-peak times stem from circadian-related deficits in inhibition. Conversely, performance may remain constant over the day in some instances, such as when tasks require mere access to or production of familiar, well learned, or practised material (e.g., vocabulary tests, simple trivial questions), or when strong, dominant responses produce correct answers (e.g., word associations, familiar category judgements).

So far, mainly inhibitory processes and a restricted set of high-order cognitive processes have been tested for possible time-of-day effects under normal working-day conditions using the chronotype-based approach. The general pattern that emerges from these studies is that synchrony effects between circadian preference and testing time can be more pronounced in elderly subjects

than in young adults (e.g., Hasher et al., 2005). These studies are reviewed in the following ageing section. Evidence from chronotype-based studies in young adults indicates time-of-day modulations of performance in inhibitory tasks (e.g., May, 1999). Given the variety of cognitive processes that can be grouped under the label "executive function", further work is needed to determine whether circadian and homeostatic drives impact on performance in other tasks of this cognitive domain.

Language

Some studies have been interested in diurnal variations linked to the processing of the rapid temporal characteristics embedded in both speech and nonspeech signals. From this perspective, these studies can be grouped under the language domain label, although such tasks also require sustained attention in order to perform efficiently. Babkoff, Zukerman, Fostick, and Ben-Artzi (2005) used a dichotic temporal order judgement task where subjects had to discriminate rapidly changing auditory stimuli, a decision ability assumed to rely on prefrontal and parietal cortex activity (Joanisse & Gati, 2003; Temple et al., 2000). Subjects exhibited higher accuracy in temporal order judgements in the morning and evening than in the early afternoon, a result discrepant with Lotze, Wittmann, von Steinbuchel, Poppel, and Roenneberg (1999) who found that order thresholds are independent of the time of day at which testing occurs. Discrepancies might be due to a reduced sample size and methodological differences in the Lotze et al. study, as well as a systematic retraining at the beginning of each session in Babkoff et al. (2005), a procedure that contributed to the stability of the data at each session.

TIME-OF-DAY PERFORMANCE MODULATIONS IN THE ELDERLY

Ageing is characterized by a series of changes at the cognitive, behavioural, and physiological levels. As explained earlier, the process of ageing interacts with the morningness-eveningness

chronotype dimension, with older adults tending to be more morning-type than younger adults. This tendency can be observed in basic real-life situations. For instance, Yoon (1997, in Hasher et al., 2005) observed that media and shopping patterns of older adults are different across the time of the day than those of younger adults, with more than 80% of the older adults reading newspapers and shopping early in the morning. On the other hand, magazines, which are mentally less demanding than newspapers, were read in the afternoon or evening by more than two thirds of the questioned subjects. These data intuitively indicate that elderly people may dedicate the morning hours—that is, their optimal testing time—to engaging in tasks that entail relatively greater cognitive or physical challenge.

Several studies have suggested that the effect of synchronicity between time of testing and preferred timing at the individual level is stronger in the elderly, so that age-related differences in performance can disappear when elderly people are tested at their optimal moment (see Hasher et al., 2005, for a review). Paradoxically, there is evidence that the influence of the circadian signal is weakened in the elderly so that this population is less susceptible to circadian and wake-dependent performance decrements (e.g., Dijk & Duffy, 1999; Münch et al., 2005). These aspects and their influence on cognitive functions are reviewed in this section.

Subjective sleepiness and basic attention in ageing

As in young adults, most studies exploring time-of-day modulations in performance in the elderly population have been concerned with basic attentional measures, from subjective statements of vigilance to more objective performance measures. An important outcome of these studies is that the process of ageing may affect the way that attentional performance is modulated by circadian and homeostatic parameters.

It is known that daytime variations in sleepiness are closely related to CBT rhythms in young adults, but results in elderly subjects were more

controversial. Indeed, whereas Hoch et al. (1992) found no difference between old and young volunteers in subjective sleepiness as assessed by the Stanford Sleepiness Scale (SSS), Monk, Buysse, Reynolds, Kupfer, and Houck (1996) observed that advancing in age alters the rhythmicity pattern of subjective alertness using a visual analogue scale as indicated by lower amplitudes of peaks and troughs, although both age groups demonstrated similar variations in the signal amplitude of the CBT rhythm. This latter result led Monk and colleagues to hypothesize that age-related changes in patterns of subjective alertness are not due to a weakness of the master circadian clock *per se* (as shown by the CBT rhythm), but rather to a weakened transduction of its output via deficits in the downstream mechanisms. However, evidence from animal studies indicates that the suprachiasmatic nucleus is subject to marked electrophysiological changes in old mice (Nygard, Hill, Wilkström, & Kristensson, 2005). Such changes in the locus of the circadian masterclock may contribute to physiological and behavioural changes associated with ageing. Converging evidence was obtained in human studies where age-related reductions have been observed in the circadian amplitude of the CBT (Dijk & Duffy, 1999) or melatonin rhythms (Münch et al., 2005). Contrary to the statements of Monk that the circadian signal was preserved with ageing, these data were interpreted as demonstrating a weaker circadian arousal signal *per se* in the elderly. Feebler variations in CBT or melatonin rhythms may be generalized to variations in attention as measured by objective performance levels, since PVT performance decrements are less susceptible to circadian and homeostatic influences in the elderly (Blatter et al., 2006). One study, however, reported the reverse pattern—that is, increased circadian variations in the rhythms of objective vigilance measure among older subjects (Buysse, Monk, Carrier, & Begley, 2005). These latter findings should be interpreted with caution since, as stated by the authors themselves, it was not clear in this study whether performance in older adults was characterized by age-related slowing rather than specific changes in circadian patterns.

Time-of-day fluctuations in cognitive performance measures in ageing

Time-of-day modulations in more complex aspects of cognitive performance have also been investigated in the elderly. Mainly, researchers have taken advantage of the general age-related shift of optimal time-of-day preference found in older adults, which means that morning peak periods are usually optimal for seniors whereas evening peak periods are more optimal in young subjects. Note that such developmental shift in circadian preference is not specific to the transition between young and older adults, but also occurs in children: Time-of-day preferences in younger children are shifted toward morningness whereas those of older children tend more toward eveningness (Hasher et al., 2005). If these preferences rhythms are associated with intellectual efforts, then the school day is structured such that achievement problems may be created for some children, particularly those who are most shifted towards eveningness. Here we focus our literature review on the differences between young and older adults.

Memory

Data indicate that synchronicity between optimal periods and the time at which testing is conducted may be a critical variable in determining age-related differences in performance on a series of cognitive tasks. Significant memory performance differences were found, for example, when younger and older adults were tested in the evening—that is, at the optimal time of day for the younger but at nonoptimal times of day for the older adults. No age-related differences were found when older and younger adults were tested in the morning—that is, at optimal time of day for the elderly, but nonoptimal time of day for the younger subjects. This was true for word span measures (Yoon et al., 1999), different long-term memory tasks, such as story recall (Winocur & Hasher, 2002), stem cued recall (May, Hasher, & Foong, 2005), sentence recognition (May et al., 1993), or false-memory paradigms (Intons-Peterson et al., 1999). Importantly, data suggest the possibility that

age-related differences can be exaggerated in the research literature when time of testing is uncontrolled. Testing time, with regard to the chronotype, may directly influence the magnitude of the observed effects and consequently artificially inflate or reduce the estimate of group differences in memory performance. Therefore, further studies investigating age-dependent changes and variability in performance should carefully control for this potential confounding factor.

It should also be noticed, however, that the picture might be more complex than a mere morning advantage for elderly people. Indeed, although May et al. (2005) observed better performance on an explicit stem completion task at peak time both for old (i.e., morning) and young (i.e., evening) adults, they also found that implicit memory on a perceptual and conceptual priming task was actually better at nonoptimal times of day for both age groups. These results leave the possibility open that explicit memory tasks that require high levels of controlled processing would be better performed at peak times when attention and arousal are high, whereas more automatic tasks would be better performed at off-peak times, when attentional control is at a lower level and cannot oppose automatic processes—for example, fluency-based familiarity in the case of perceptual priming.

Data reported above give evidence that explicit memory tasks where high levels of controlled processing are required would be better performed at peak times when attention and arousal are high. Since executive functions are defined as a series of mechanisms that explicitly control the content and evolution of cognitive processes, similar effects could be expected in this cognitive domain.

Executive functions

Inhibitory processes are largely sensitive not only to ageing (Van der Linden & Collette, 2002), but also to time-of-day effects under normal daily-life conditions (see above). Indeed, in chronotype-based studies consistent time-of-day effects on performance measures have been found in both young and elderly adults for inhibitory control over no-longer-relevant thoughts or

unwanted but potent responses, perceptual inhibition, the ability to inhibit distractors in problem-solving tasks, inhibitory efficiency of working memory, and susceptibility to distraction (May, 1999; May et al., 1998; Intons-Peterson et al., 1998; West et al., 2002). These studies indicate that subjects tested at nonoptimal times according to their chronotype exhibited performance deterioration relative to optimal testing times. Furthermore, it was shown that age-related deterioration in inhibitory processes, which can already be observed at optimal testing time, is significantly more severe when older adults are tested at their nonoptimal time.

In the elderly, testing time exerts such an influence on the pattern and magnitude of age-related differences in inhibitory tasks that age-related impairment can be small and even undetectable when assessed in the morning (the optimal time of day in most elderly persons), but become consistently robust in the evening. Accordingly, Intons-Peterson et al. (1998) observed a negative priming effect similar to that of younger people in older adults when tested at their preferred time, whereas this effect was absent when elderly adults were tested at their nonpreferred times of day. However, Li, Hasher, Jonas, Rahhal, and May (1998) did not observe age-related differences attributable to the time of testing in a reading aloud task challenging inhibitory capacities. A possible explanation proposed by the authors for this lack of an effect is that reading aloud in the face of distraction is an everyday condition for most people. Thus, high skill levels at a given task may provide a boundary condition for synchrony effects (i.e., high skill levels may enable performance to be invariant across optimal and nonoptimal testing times). An alternative hypothesis would be that higher intraindividual performance variability, typically observed in cognitive ageing (see Morse, 1993, for a review), partially explains time-of-day variations in cognitive performance. However, Murphy and colleagues (Murphy, West, Armilio, Craik, & Stuss, 2007) failed to disclose any relationship between intraindividual memory performance variability and circadian arousal parameters in a group of elderly adults.

The influence of time of day on *flexibility capacities* was investigated using the Trail Making Test (TMT) in elderly adults with discrepant results (Brown, Goddard, Lahar, & Mosley, 1999; May & Hasher, 1998). In a correlational study, Brown et al. (1999) reported that time of day of testing did not predict performance on a particular version of the TMT in different age groups. On the other hand, May and Hasher (1998) reported time-of-day modulations in flexibility measures of TMT performance in older adults, but not for baseline performance in the nonalternating part of the TMT.

In a more clinical context, Paradee, Rapport, Hanks, and Levy (2005) administered a neuropsychological testing battery in a population of middle-aged (mean age of 61 years) morning-oriented rehabilitation inpatients with cognitive and noncognitive impairment. Again, results disclosed a close relationship between cognitive performance, circadian preference, and time of testing. For the individuals with a cognitive impairment, testing at nonpreferred time was more challenging than that for cognitively intact patients. In line with previous studies (e.g., Intons-Peterson et al., 1999; May, 1999; May et al., 1993; West et al., 2002), consistent effects of testing time and circadian preference were observed for tasks of executive function, including working memory, flexibility and set shifting, and tasks incorporating similar complex, higher order processing demands (e.g., copying a complex figure), but not for other tasks (e.g., vocabulary tasks, familiar judgement tasks) with lower and/or less complex cognitive demands. The results of this study support the notion that not all cognitive processes are equally affected by time of day and that performance seems unaffected by the time of day for tasks simply requiring access to routine answers (Yoon et al., 1999). It also emphasizes the clinical importance of taking time of day and the individual's circadian preference into account when assessing cognitive functions.

Finally, *planning performance* is one of the only executive function components that have been investigated in the elderly under controlled constant routine (CR) conditions so far with

additional manipulation of sleep pressure. In this study, Blatter et al. (2005) administered parallel versions of a maze-tracing planning task with two difficulty levels at 2-hr intervals during a 40-hr protocol interspersed with naps (low sleep pressure) or wakefulness (high sleep pressure) episodes. In line with previous reports (see above sections), results showed that circadian timing influenced planning performance, as it started slowing down when the waking period exceeded the normal daily amount of hours spent awake (i.e., ~16 hr), with a circadian performance trough at 8 a.m. Additionally, they found that circadian timing influences planning performance only when the level of difficulty was high, which was discrepant with a prior study (Bonnefond, Rohmer, Hoeft, Muzet, & Tassi, 2003) reporting deteriorated performance in a visual discrimination task in older adults during the night, but not in a more complex descending subtraction task. One may notice, however, that visual discrimination has a natural limit in the perceptual system, whereas subtraction is a cognitive operation that can be trained. Therefore, as also surmised by the authors, the subtraction task is more susceptible to a practice effect, which—if not controlled—may have masked the impact of intrinsic circadian variations on performance.

GENERAL DISCUSSION

In this review, we have attempted to summarize studies focused on the effects of sleep pressure, circadian variations, chronotype, and ageing on cognitive functioning. These studies are listed in Table 1 for an overview. The picture that emerges from this survey is that, beyond physiological variables, time-of-day modulations affect performance on several cognitive tasks and that these performance fluctuations are additionally contingent upon interindividual differences in circadian preference.

It appears from these studies that some cognitive processes are particularly vulnerable to variations in the circadian arousal level, whereas others are less or even apparently not affected.

However, it remains unclear whether different tasks, involving diverse cognitive processes or differing in difficulty, exhibit genuine differences in time-of-day modulations. One important outcome of the studies reported above is that a couple of between-task differences in the time course of performance can be explained when taking the use of more or less controlled research paradigms into account. Indeed, many differences observed in daytime settings (e.g., chronotype based) fail to appear when data collection is extended beyond the normal waking-day duration into the night (CR) or when non-sleep-deprived subjects are tested at all circadian phases (FD paradigm; e.g., Cajochen et al., 1999; Monk, 1997; Wright et al., 2002; Wyatt et al., 1999). Under these conditions, performance consistently parallels CBT variations. However, and given the relative paucity in the number and variety of studies conducted so far in this domain, a strict parallelism between time-of-day fluctuations in cognitive performance measures and body temperature cannot be generalized. With the exception of the PVT measure and some subjective alertness scales, most studies have used what they have called “cognitive throughput” performance measures—that is, multidetermined cognitive tests such as the digit symbol substitution task. As shown above, one of the rare studies investigating more complex executive functions (i.e., the maze planning task) under controlled conditions actually disclosed a differential effect of task complexity on circadian performance fluctuations in the elderly (Blatter et al., 2005). Therefore, drawing more definite conclusions requires engaging on thorough studies dedicated to the investigation of time-of-day effects on the different levels of cognitive processing, while simultaneously controlling for circadian and homeostatic parameters.

There are different levels of explanation for circadian or time-of-day modulations. As previously proposed, one could argue that circadian fluctuations in cognitive functioning are merely the reflection of temporal variations in subjective sleepiness or alertness, which are closely linked to the duration of prior wakefulness and to circadian phase variations (Czeisler et al., 1985; Monk, 1987). In other

Table 1. Overview of recent researches interested in time-of-day effects on cognition, classified by cognitive domain, applied paradigm, and age groups

<i>Age group</i>	<i>Cognitive domain</i>	<i>Test</i>	<i>Paradigm</i>	<i>Global results</i>	<i>Study</i>
<i>Attentional capacities</i>					
Young	Alertness(tonic and phasic)	Continuous performance test	Constant routine	Circadian variation in alertness measures	Valdez et al., 2005
	Vigilance/sustained attention	PVT, ADD, Mackworth Clock Test	Constant routine/ Forced desynchrony	Parallelism to core body temperature when testing is extended into the biological night	Johnson et al., 1992 Dijk et al., 1992 Cajochen et al., 1999 Wyatt et al., 1999 Wright et al., 2002 Monk et al., 1996 Valdez et al., 2005
		Continuous performance test	Constant routine	No circadian variation in vigilance measures	Valdez et al., 2005
		Number facility test	Normal working day	Performance peak at noon	Kraemer et al., 2000
	Subjective vigilance	Sleepiness scales (VAS, KSS)	Constant routine/ sleep deprivation	Parallelism to objective vigilance measures	Gillberg et al., 1994 Dijk et al., 1992 Cajochen et al., 1999 Monk et al., 1996 Wyatt et al., 1999
			Forced desynchrony	Parallelism to objective vigilance measures	Wyatt et al., 1999
			Sleep deprivation	Discrepancy between objective and subjective vigilance measures	Leproult et al., 2003
	Physiological measures	Pupillometry, MSLT	Normal working day	Peak levels immediately after getting up and again in the early evening	Kraemer et al., 2000
		Binocular double-pulse test	Constant routine	Peak around midday	Lotze et al., 2000
	Selective attention	Letter cancellation task	Sleep deprivation	Parallelism to core body temperature especially when increased number of targets	Casagrande et al., 1997 De Gennaro et al., 2001 Mickulincker et al., 1988
		Visual discrimination task	3 testing times (morning-evening-night)	Time of day effect for both age groups	Bonnefond et al., 2003
		Visual search tasks	Constant routine preceded by a 7-day rotating-shift work simulation	Effects of the circadian pacemaker and homeostatic sleep drive on global vigilance measures strikingly different from effects on selective attention	Horowitz et al., 2003

(Continued overleaf)

Table 1. (Continued)

<i>Age group</i>	<i>Cognitive domain</i>	<i>Test</i>	<i>Paradigm</i>	<i>Global results</i>	<i>Study</i>
Old	Vigilance	Mackworth Clock Test	Normal working day	Decrements among the elderly on morning and evening	Hoch et al., 1992
		Manual dexterity task	Sleep deprivation	Increased circadian variation in older adults	Buysse et al., 2005
		Wilkinson 4-Choice Reaction Time task	Sleep deprivation	Increased circadian variation in older adults	Buysse et al., 2005
		PVT	Constant routine	Decreased circadian amplitude in older adults	Blatter et al., 2006
		Mackworth clock procedure	Constant routine	Decreased circadian amplitude in older adults	Monk & Kupfer, 2000
	Subjective vigilance	Sleepiness scales	Normal working day	Absence of correlation between sleepiness measures and performance patterns	Hoch et al., 1992
			Constant routine	Alteration of the circadian rhythmicity pattern	Monk et al., 1996
		60-hr nap protocol under constant routine	Lower level, and smaller circadian variations compared to young subjects	Buysse et al., 2005	
			Sleep deprivation	Discrepancy between objective and subjective vigilance measures	Leproult et al., 2003
			Physiological measures	MSLT	Normal working day
Young	Working memory	Serial search task	Normal working day	Differential modulation according to working-memory load	Folkard et al., 1976 Mikulincer et al., 1989
			Constant routine	Parallel to core body temperature independent of working-memory load	Monk et al., 1996
		DSST	Constant routine	Parallelism to core body temperature	Cajochen et al., 1999 Wyatt et al., 1999 Wright et al., 2002
		Phonological working-memory task	Constant routine	1-hr phase delay with respect to the endogenous core body temperature rhythm	Ramirez et al., 2006
		Digit Span	Normal working day	No time of day effect	Hidalgo et al., 2004
		Visual working-memory task	Constant routine	3-hr phase delay with respect to the endogenous core body temperature rhythm	Ramirez et al., 2006

(Continued overleaf)

Table 1. (Continued)

<i>Age group</i>	<i>Cognitive domain</i>	<i>Test</i>	<i>Paradigm</i>	<i>Global results</i>	<i>Study</i>
		Descending subtraction	3 testing times (morning-evening-night)	No time-of-day effect	Bonnefond et al., 2003
	Declarative memory	Memorization of prose passages	Constant routine/forced desynchrony	Parallelism to core body temperature	Johnson et al., 1992
			Normal working day (chronotype based)	Synchronization between chronotype and performance; largest effect on difficult condition	Petros et al., 1990
		Word pair learning	Constant routine	Parallelism to core body temperature	Cajochen et al., 1999 Wyatt et al., 1999 Wright et al., 2002
		Old-new recognition	Normal working day	Overall better recognition in the evening than in the morning	Koulack 1997
		Word pair learning	Normal working day	Performance increase over the day during the recall one specific word list; independent of chronotype	Hidalgo et al., 2004
		Visual memory (building test)	Normal working day	No time-of-day effect	Hidalgo et al., 2004
	Procedural memory	SRT	Constant routine	Circadian modulation in all performance measures of sequence learning	Cajochen et al., 2004b
Old	Declarative memory	Verbal recognition	Normal working day (chronotype based)	Only age-related differences in performance in the late afternoon	May et al., 1993
		Stem completion	Normal working day (chronotype based)	Synchrony effect in older and younger subjects	May et al., 2005
		False memory	Normal working day (chronotype based)	Synchrony effect in older, but not in younger adults	Intons-Peterson et al., 1999
	Prospective memory	Medical appointment task	Normal working day (chronotype based)	Time-of-day differences in medical adherence (morning > evening)	Leirer et al., 1994
	Implicit memory	Priming	Normal working day (chronotype based)	Better performance at off-peak times for both age groups	May et al., 2005
			<i>Executive functions</i>		
Young	Information update	n-back	Constant routine	Linear performance decrease during the diurnal hours, steady increase in the morning hours	Van Eekelen et al., 2003
	Dual-task processing	Dual task	Constant routine	Linear performance decrease during the diurnal hours, steady increase in the morning hours	Van Eekelen et al., 2003

(Continued overleaf)

Table 1. (Continued)

<i>Age group</i>	<i>Cognitive domain</i>	<i>Test</i>	<i>Paradigm</i>	<i>Global results</i>	<i>Study</i>
		Dichotic temporal order judgement	Sleep deprivation	Higher accuracy in the morning and evening than in the early afternoon	Babkoff et al., 2005
	Flexibility	Phonological fluency	Sleep deprivation Normal working day	No time-of-day effect No time-of-day effect	Lotze et al., 1999 Hidalgo et al., 2004
	Inhibition	Go/no-go	Normal working day	Time of day effect only for controlled aspects of the task	Manly et al., 2002
		Social judgement	Normal working day (chronotype based)	More stereotypic biases when judgments made at nonoptimal time of day	Bodenhausen, 1990
Old	Planning performance	Maze tracing	Constant routine	Circadian timing in performance when the task was sufficiently difficult	Blatter et al., 2005
	Inhibition	Garden-path procedure	Normal working day (chronotype based)	Synchrony between circadian arousal and testing time in performance for both age groups	May & Hasher, 1998
		Stop signal paradigm	Normal working day (chronotype based)	Synchrony between circadian arousal and testing time in performance; affection of age differences	May & Hasher, 1998
		Stroop	Normal working day (chronotype based)	Synchrony between circadian arousal and testing time in performance for elders	May & Hasher, 1998
		Inhibition of distractors	Normal working day (chronotype based)	Synchrony between circadian arousal and testing time in performance for both age groups	May & Hasher, 1999
		Inhibition in working memory	Normal working day	Time of day effect in the access, deletion and response inhibition function in both age groups	West et al., 2002
		Reading-aloud task with distractors	Normal working day (chronotype based)	No time-of-day effect	Li et al., 1998
		Negative priming	Normal working day (chronotype based)	Negative priming only at optimal testing times for both age groups	Intons-Peterson et al., 1998
	Flexibility	TMT	Normal working day (chronotype based) Normal working day (chronotype based)	Synchrony between circadian arousal and testing time in performance for elders No time-of-day effect	May & Hasher, 1998 Brown et al., 1999

Note: PVT = Psychomotor Vigilance Task. ADD = attention-deficit disorder. VAS = Visual Analogue Scale. SSS = Stanford Sleepiness Scale. MSLT = Multiple Sleep Latency Test. DSST = Digit Symbol Substitution Task. SRT = serial reaction time. TMT = Trail Making Test.

words, this hypothesis proposes that daily fluctuations in cognitive functions would reflect the circadian modulation of general arousal patterns. However, this simple assumption cannot be fully endorsed, since available data indicate that performance rhythms do not systematically reflect the univocal and direct result of diurnal changes in physiological parameters, nor can they be predicted by subjective measures of arousal (e.g., Blatter et al., 2005; Casagrande et al., 1997; Frey et al., 2004; Owens et al., 1998; West et al., 2002). For instance, Blatter et al. (2005) showed that basic attentional performance measures, as indexed by PVT performance, have no predictive power for performance levels on tasks challenging executive functions. Although attention can be conceptualized as a global function that is necessary for the optimal processing of most cognitive tasks (Blatter et al., 2005) and that additionally varies with increasing cognitive load (Stipacek, Grabner, Neuper, Fink, & Neubauer, 2003), attention is not the exclusive factor related to performance modulation. Hence, even if there is both task- and circadian-related adaptation in basal arousal and vigilance for optimal performance (Bonfond et al., 2003), these are not the only necessary and sufficient parameters subtending circadian modulation in cognitive functioning.

In contrast to the idea that cognitive performance is indirectly modulated over the day by fluctuations in basic arousal parameters, it may be assumed that cognitive processes per se are specifically modulated by time of day. Indeed, above attentional processes, the current literature review suggests that higher order cognitive functions, mainly executive control or working-memory load, are processes that appear intrinsically sensitive to time-of-day modulations. For instance, tasks involving active control over response (i.e., executive control) have been found to be more sensitive to time of testing and circadian preference than are other tasks that merely require access to or production of familiar, well-learned material, particularly during ageing. Similar patterns can be applied to rehabilitation inpatients, where increased vulnerability of timing preference, particularly for cognitively impaired patients, has been observed for tasks involving control over response

(Paradee et al., 2005) revealing the clinical importance in considering testing times.

A plausible hypothesis would be that age-related differences in time-of-day modulation on cognitive functioning can be explained in the framework of an inhibition-based model (e.g., May & Hasher, 1998; West et al., 2002). In this model, inhibitory processes support efficient working memory by limiting access of irrelevant information into and deleting no-longer-relevant information from working memory and/or by inhibiting prevalent responses. These processes appear highly sensitive to circadian preference and testing time, and even more in the case of ageing, which may explain the predominant impact of these parameters on executive control functions. Data gathered in the memory domain also indicate that explicit performance is better for all age groups at their optimal testing time, whereas implicit priming performance may be better at the nonoptimal daytime according to the individual's chronotype. These results may also fit with the inhibition-based model (e.g., Stoltzfus & Zacks, 1996), since inhibitory processes are proposed to support efficient strategic processes involved in explicit recollection, at least under normal daily conditions.

Although ageing seems to be associated with a reduction in the amplitude of circadian patterns, time of day of testing appears tremendously crucial in elderly populations. This may have important repercussions both for the clinical management of aged neuropsychological patients and for the interpretation of the experimental results gathered in these populations. Indeed, differences in performance measures between younger and older adults increase, or even only appear, when aged subjects are tested at their nonoptimal time of day (Hasher et al., 2005). Conversely, age differences reported for several performance measures are attenuated when older adults are tested during their optimal time and younger adults during their nonoptimal time (May et al., 1993). Troubling here are evidences that studies examining age differences in several cognitive domains are frequently scheduled to afternoon hours, so that young persons are tested at optimal times, whereas older adults are tested at their nonoptimal times (May et al., 1993). This suggests that the

size of age difference in cognition may be exaggerated as compared to results obtained when all participants are tested near their optimal time of day.

However, interpretation of results is highly dependent upon the context in which data have been gathered. Indeed, many of these studies were actually based on the chronotype approach, and therefore the influence of the sleep–wake cycle on time-of-day performance modulations was not controlled. For instance, one may hypothesize that results observed in studies carried out under normal day–night conditions and scheduling their testing time according to the external clock time are partially explained by confounding factors such as interindividual differences in phase position on the circadian curve during testing time, in sleep pressure or in sleep inertia. The few studies conducted under better controlled conditions found a linear decline over 36 hours of wakefulness (CR paradigm) in aged subjects for various parameters (e.g., affect, activation, visual search speed, verbal reasoning speed, manual dexterity, vigilance hit rate, etc.), without or at least with a strongly attenuated superimposed 24-hr rhythmicity that is normally found in young subjects (e.g., Cajochen, Knoblauch, Krauchi, Renz, & Wirz-Justice, 2001; Dijk & Duffy, 1999). Whether this alteration is determined by the time elapsed since awakening (Dijk & Duffy, 1999), by the rhythmic inputs from the endogenous circadian pacemaker (Cajochen et al., 2001) per se, or by a deficit in the transduction of its output (Monk et al., 1996) still remains an open question. Furthermore, the circadian preference (chronotype) profile is not representative of, but rather superimposed on, the general circadian pattern of sleep propensity that parallels the CBT curve over the 24-hr day. Consequently, even if the circadian signal is truly weakened at the physiological level in older adults, they may not have sufficient cognitive reserve to cope efficiently enough with the heightened demand of performing at a nonoptimal moment. Accordingly, Paradee et al. (2005) found that participants without cognitive impairment performed better on a task requiring sustained attention when tested during the normal waking day at their nonpreferred as opposed to their preferred times. It could be hypothesized that younger adults respond

to heightened cognitive demands when performing at a nonoptimal time by intensifying their efforts, in line with theories that view cognitive reserve as the capacity of a subject to enhance brain network efficiency in response to increased requirements (Stern et al., 2003). However, this assumption has to be reconciled with observations from Blatter et al. (2005) who showed that sleep deprivation is more detrimental to performance in the young than in the elderly subjects.

Finally it must be accounted that ageing and frequently associated pathologies are characterized by significant changes in general sleep and circadian patterns (e.g., Wolkove, Elkholy, Baltzan, & Palayew, 2007). It is well known that ageing contributes to the deterioration in sleep quality and the increased incidence of reported sleep disturbances (e.g., Van Cauter, Plat, Leproult, & Copinschi, 1998). For instance, we cannot neglect the fact that elderly persons are more frequently used to day-time napping (Dinges, 1989; Monk, Buysse, Carrier, Billy, & Rose, 2001), which probably influences the time course and characteristics of the circadian pacemaker, the ensuing sleep-dependent cycle, and their respective influence on cognitive functioning. Similarly, sleep disturbance is a frequent symptom in patients clinically diagnosed with age-associated, neurodegenerative dementias such as Alzheimer's disease (e.g., Loewenstein et al., 1982) or other neurological affliction such as diffuse Lewy body disease (Grace, Walker, & McKeith, 2000). Sleep disturbances and shifts in daytime patterns often precipitate decisions by families and caregivers to seek institutional care (Pollak & Perlick, 1991). Patients diagnosed with probable Alzheimer disease also exhibit circadian disturbances, including reduced amplitudes and phase delay of circadian variation in CBT and activity, and likewise older adults (van Someren et al., 1996). Additionally, brain damage itself seems to impact both on the circadian and homeostatic processes. A review of these effects is beyond the scope of the present review. How these alterations contribute to time-of-day fluctuations in performance measures still remains an open debate, the outcomes of which will be critical for clinical neuropsychologists. Furthermore, advancing age and neurological disease are characterized by increasing

variability in cognitive performance. Although the debate remains to be clarified, available data at least advocate the importance to control for time-of-day parameters when attempting to draw comparisons between age groups. This could probably be generalized to developmental studies in children, as circadian and sleep patterns are known to evolve especially with the shift from childhood to adolescence (Hasher et al., 2005).

To sum up this review, we know that daily rhythms in sleep behaviour and waking performance are generated by the interplay of multiple external and internal oscillators. We also know that sleep and performance cannot be predicted by either oscillator independently but critically depend on their own characteristics and relationships (Dijk & von Schantz, 2005). What is still less well known, although trends can be identified, is whether and to what extent specific cognitive parameters are particularly vulnerable to time-of-day variations and whether different cognitive variables follow differential modulation curves. Notwithstanding, a few bottom lines can be drawn. First, synchrony between individual preferences and time of testing is a dominant effect. It seems that only highly practised responses are invariant across the day—all other responses being susceptible to the time-of-day effect during normal day–night conditions since they require a certain degree of control over stimuli and responses. Second, large differences in the circadian cycles between young and older adults have been reported. An accurate assessment of the way that cognition declines in ageing requires that researchers or clinicians pay attention to the time when participants are tested. A lack of consideration in testing time can lead to an exaggeration of age differences (see Hasher et al., 2005, for a review). These evidences should be considered in future research in cognitive psychology and neuropsychology. At the fundamental research level, it remains to ascertain the respective contributions of the homeostatic and circadian processes, as well as the individual chronotype and of the ageing process, on time-of-day fluctuations in cognitive performance. This leaves broad and exciting perspectives for numerous and fruitful experiments that would eventually lead to a better understanding of how cognitive

processes are modulated and would significantly change the way that we will schedule and conceptualize our research and patient's evaluations in clinical settings.

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APPENDIX A

List of abbreviations

- C = Circadian process according to the two-process model of sleep–wake regulation
 CBT = Core body temperature
 CR = Constant routine protocol
 FD = Forced desynchrony protocol
 KSS = Karolinska sleepiness scales
 MEQ = Morningness–Eveningness Questionnaire
 PVT = Psychomotor Vigilance Task
 S = Homeostatic process according to the two-process model of sleep–wake regulation
 SSS = Stanford Sleepiness Scale
 SCN = Suprachiasmatic nucleus
 TMT = Trail Making Test
 VAS = Visual Analogue Scale