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Circadian Rhythms in Fatigue, Alertness and Performance

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Introduction

Both wakefulness and sleep are modulated by an endogenous regulating system, the biological clock, located in the suprachiasmatic nuclei of the hypothalamus. The impact of the biological clock goes beyond compelling the body to fall asleep and to wake up again. The biological clock also modulates our hour-to-hour waking behavior, as reflected in fatigue, alertness and performance, generating circadian rhythmicity in almost all neurobehavioral variables.

Before focusing on circadian rhythmicity in waking functions, it is appropriate to give a brief description of the three variables mentioned in the title of this chapter. In the literature, various definitions of fatigue, alertness and performance can be found (e.g., [1, 2]) and differences of opinion exist about their meaning. For the purposes of this chapter, the term *performance* comprises cognitive functions ranging in complexity from simple psychomotor reaction time, to logical reasoning, working memory and complex executive functions. By *alertness* is meant selective attention, vigilance, and attentional control (after [3]). *Fatigue* refers to subjective reports of loss of desire or ability to continue performing. Additionally, *subjective sleepiness* is used here for subjective reports of sleepiness or the desire to sleep.

The meanings of fatigue and subjective sleepiness given above express the relationship that exists between alertness and performance during wakefulness on the one hand and sleep on the other hand. The interaction of the circadian and sleep-wake systems in regulating fatigue, alertness and performance is described in the second part of this chapter. It is important to note that this chapter does not cover sleep propensity [4, 5], but rather focuses on circadian regulation in effortful performance and its corresponding subjective states.

Circadian rhythmicity

Subjective measures of fatigue and alertness

Many techniques are available for the detection of circadian rhythmicity in neurobehavioral variables. Successful results have been reported in studies with a wide array of subjective measures of alertness and fatigue. These have been obtained with, for instance, visual analogue scales (VAS; [6]) and Likert-type rating scales such as the Stanford Sleepiness Scale (SSS; [7]), the Karolinska Sleepiness Scale (KSS; [8]), the Activation-Deactivation Adjective Check List (AD-ACL; [9]), and the Profile Of Mood States (POMS; [10]).

Subjective measures of fatigue and alertness in particular are vulnerable to numerous confounding influences, however, which can *mask* their distinct circadian rhythmicity. Masking is a critical concept to understand when considering the assessment of circadian rhythms in neurobehavioral variables. Masking refers to the evoked effects of non-circadian factors on the measurements of circadian rhythmicity. The *context* in which such measurements are taken (i.e., the environmental and experimental conditions) is a major source of masking effects. Masking can both obscure a circadian rhythm, or create the appearance of a circadian rhythm. Masking factors may include the following: demand characteristics of the experiment [11], distractions by irrelevant stimuli [12], boredom and motivational factors [13, 14, 15], stress [16], food intake [17], posture [18], ambient temperature [14], background noise [19], lighting conditions [20], and drug intake (e.g., caffeine).

Physical and mental activity can be masking factors as well, as illustrated in figure 1, where the effects of performance tests on subjective estimates of alertness become apparent at certain circadian phases during sleep deprivation. In this example, subjects reported feeling less

alert after being challenged to perform. This suggests that prior activity can influence subjective estimates, and that it can contaminate circadian effects if not properly controlled when measuring circadian rhythmicity in subjective states.

Place figure 1 about here.

Prior wakefulness and sleep can also be considered masking factors when it comes to observing circadian rhythmicity in neurobehavioral variables. Sleep and sleep loss have large effects on alertness and performance. These issues are illustrated in the second half of the chapter. Despite potential masking factors and their interactions, subjective scales have been used to index circadian rhythmicity, by applying them repeatedly across the day under carefully controlled conditions [21, 22].

Performance measures

Rather than relying on subjective measures, many studies of circadian rhythms have relied on objective performance measures. For example, studies have employed search-and-detection tasks [23, 24], and simple and choice reaction time tasks [25] to obtain objective measures of circadian variation in performance. Typically, the speed and the accuracy of responses to a series of repetitive stimuli are analyzed.

There are many performance outputs that have been conceptually distinguished, including simple sorting [26], logical reasoning [27], memory access [28], and more complex activities such as school performance [29] and meter reading accuracy [30]. Various tasks have been

used to study circadian variation in these different aspects of performance. A number of studies have concluded that different tasks [31, 32] and different task parameters [33, 34, 35] may yield different peak phases of circadian rhythmicity. This has led to the speculation that there are many different circadian rhythms and many different clock mechanisms controlling them [36, 37]. Under strictly controlled laboratory conditions, however, most of the inter-task differences disappear [38, 39]. As illustrated in figure 2, it can generally be stated that under such conditions, the circadian rhythms of cognitive and psychomotor performance covary with subjective sleepiness. Furthermore, these rhythms mimic the circadian rhythm of core body temperature, which has been demonstrated to be a good marker of the biological clock. Roughly, high and low body temperature values correspond to good and poor performance, respectively [39, 40, 41].

Place figure 2 about here.

The mid-afternoon dip

In addition to the circadian covariation of neurobehavioral variables with core body temperature, in some individuals there appears to be a short-term dip in these variables in the afternoon, that has been referred to as the mid-afternoon, siesta, post-lunch, or post-prandial dip (even though it appears to have no relationship to food intake). This dip has been observed in field studies (e.g., [30]) and in controlled laboratory experiments (e.g., [42]). However, it is not consistently found (e.g., [43, 44]).

The most compelling evidence for the existence of a mid-afternoon dip comes from studies

on sleep propensity [45, 46] and on the timing of daytime naps [47]. Yet, there is little evidence for a consistent mid-afternoon dip in performance measures. Consequently, the phenomenon of a mid-afternoon increase in sleep propensity that does not necessarily express itself in performance deficits is poorly understood, and its relationship with the biological clock remains unknown. Field studies of human performance have been used as evidence for the existence of a mid-afternoon dip in performance [48], but such data cannot be used as positive evidence due to the uncontrolled influence of differential amounts of activity by varying numbers of people over time (i.e., exposure), which may confound these studies.

The practice effect and other artifacts

A problem that limits the reliability of task performance for the assessment of circadian rhythmicity in alertness and fatigue, is the well-known practice effect. This is illustrated in figure 3, which shows cognitive performance improving across three consecutive days. The practice effect is difficult to distinguish from the circadian rhythm, but this dilemma might be circumvented by testing subjects in different orders across times of day. The practice effect is then balanced out by averaging over subjects. This assumes that the practice effect and the circadian rhythm are additive and have the same relationship in every subject. Since this assumption is often untested, it remains unclear whether practice effects on cognitive tests can be averaged out. A better way to deal with this problem is by training subjects to asymptotic performance levels before attempting to assess circadian rhythmicity.

Place figure 3 about here.

Practice effects are not the only masking factors that may conceal, accentuate, or otherwise distort circadian rhythmicity in task results. Many of the same variables that serve to mask circadian rhythmicity in subjective estimates of fatigue and alertness, also can mask circadian variation in performance. The effects of masking can vary from changes in the range of circadian variation to changes in the shape of the circadian curve; even total concealment of the circadian rhythm is possible (cf. figure 3, where sleep prevents measurement of nocturnal performance and the practice effect obscures measurement of diurnal performance). Thus, it is not easy to extract meaningful information about the amplitude (i.e., magnitude) and the phase (i.e., timing) of the circadian rhythm in performance measures without an understanding of the masking effects that influence these variables.

In comparison to subjective alertness and fatigue, circadian rhythmicity in cognitive performance is more complicated to assess. Not only is performance often affected by learning, aptitude, and other masking factors (e.g., lighting, background noise, as listed above), but it is also affected by the parallelism of the various brain processes that regulate performance. As an example, it has been reported that subjects may change their performance strategy on a task by invoking subvocalization, in a rhythmic, circadian pattern [49]. This example illustrates that it can be difficult to distinguish the circadian rhythm in task performance *per se* from that of corresponding changes in performance strategy. The same applies to compensatory effort (that is, increased effort to keep up performance). Furthermore, the effect of compensatory effort may be enhanced if subjects are informed about their results during a performance task.

Electroencephalographic measures

The circadian rhythm in task performance is believed to reflect functional changes in the brain. The electroencephalogram (EEG) and brain potentials associated with the reaction to a stimulus, which are called evoked potentials or event-related potentials (ERP), have been used as a measure of alertness. In order to average out the background EEG, many ERP measurements must be taken (i.e., many stimuli must be offered) consecutively. Therefore, ERPs are usually recorded during repetitive search-and-detection and reaction time tasks. Diurnal changes in the amplitude and the location of ERP waves have been interpreted as reflecting circadian variations in alertness [50, 51]. Hemispheric differences have been detected [52], suggesting separate circadian rhythms for the left and right hemisphere. However, masking from a variety of sources presents a problem in the interpretation of such ERP data (e.g., [53]).

Circadian variations in alertness have also been associated with changes in the background EEG during wakefulness. The amount of alpha activity (i.e., EEG activity in the frequency band from 8 Hz to 12 Hz) in the resting EEG with eyes held either open or closed (to avoid artifacts from blinking) is thought to be related to the level of alertness [54]. Unfortunately, difficulties in the recording, analysis and interpretation of the alpha band [55] and other EEG frequency bands [56] have substantially limited its usefulness. Furthermore, it has been shown that significant effects in the EEG occur primarily when alertness is much lower than what is normally encountered at the trough of circadian variation, such as when subjects are sleep deprived [8, 57]. This has also been reported for slow-rolling eye movements (SEMs) in the electro-oculogram (EOG), which have been used as an electrophysiological measure of alertness as well [8].

Another way in which the EEG has been used, is to measure the latency with which subjects fall asleep (i.e., sleep propensity) at various times of day. These sleep latency tests include the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT) as well as many variations of these paradigms. The sleep latency tests have been well documented to be sensitive to sleep loss and pathological conditions, and are covered elsewhere in this text.

Inter-individual differences

Inter-individual differences in circadian amplitude, circadian phase, and mean performance level are reported throughout the literature. Occasionally inter-individual differences in the circadian period (τ) have been reported as well (e.g., [58]), but it should be emphasized that under normal entrained circumstances τ equals 24 h.

Morningness/eveningness (i.e., the tendency to be an early “lark” or a late “owl”) is the most substantial source of inter-individual variation. Morning- and evening-type individuals differ endogenously in the circadian phase of their biological clock [59]. This is echoed in the diurnal course of their neurobehavioral variables (as reviewed in [60, 61]). Some people are consistently at their best in the morning, whereas others are more alert and perform better in the evening. There is reason to believe that this difference in circadian phase preference and its reflection in neurobehavioral functions is a more or less enduring trait. To the extent that this is the case, it may be seen as a phenotypic aspect of the circadian rhythmicity in humans.

Other, less substantial sources of inter-individual variation in the circadian rhythmicity of alertness and performance include personality (e.g., introversion/extraversion) and age. No consistent relevance of gender has been reported.

Circadian rhythmicity interacts with sleep and wakefulness

Sleep deprivation

Considerable research effort has been put into *unmasking* the circadian rhythm, that is, eliminating sources of extraneous variance in order to expose the “pure” circadian rhythm in variables, including alertness and performance. In particular, the constant routine procedure [62] and its modifications are generally regarded as the gold standard for measuring circadian rhythmicity. By keeping subjects awake with a fixed posture in a constant laboratory environment for at least 24 h, circadian rhythms in a host of physiological and neurobehavioral variables can be recorded (see figure 2). Indeed, for body temperature, the circadian rhythm is believed to be free of masking effects.

However, masking factors can differ greatly among variables. In particular, when neurobehavioral variables are considered, the elimination of sleep (i.e., sleep deprivation) and the stimuli delivered to sustain wakefulness can constitute masking factors. In fact, in constant routine experiments these masking effects have become evident in subjective measures of alertness and fatigue [57, 59, 63]. Figure 2 shows the somewhat reduced values for subjective alertness, and cognitive and psychomotor performance after 30 h awake in the constant routine, as compared to the values of these variables 24 h earlier (i.e., at the same circadian phase but without sleep deprivation).

Typically, superimposed on the circadian rhythm in a given variable there is also a progressive change that is associated with the time spent awake (e.g., [64]). When total sleep deprivation is continued for several days (whether in a constant routine procedure or an experimental design involving ambulation), the detrimental effects on alertness and performance grow, and

although the circadian process can thus be exposed, it is overlaid on an almost linear change reflecting increasing homeostatic pressure for sleep (e.g., [65, 66]). This is illustrated in figure 4 for performance lapses on a psychomotor vigilance task.

Place figure 4 about here.

Sleep–wake regulation

The circadian modulation of alertness and performance that appears to be superimposed on monotonic changes during sleep deprivation has prompted efforts to mathematically model the processes involved. The two-process model of sleep–wake regulation [67, 68] has been applied to the understanding of the temporal profile of neurobehavioral functioning across days of sleep deprivation. The model consists of a *homeostatic* process (process S) and a *circadian* process (process C), which combine to determine the timing of the onset and offset of sleep. The homeostatic process represents the drive for sleep that increases during wakefulness (as can be felt when wakefulness is maintained beyond the habitual bedtime into the night) and decreases during sleep (symbolizing the neurobehavioral recovery obtained from sleep). When the “homeostat” increases above a certain level, sleep is triggered; when it decreases below a lower level, wakefulness is invoked. The circadian process represents the daily oscillatory component in the drive for sleep and wakefulness. In particular, it has been suggested that the circadian system actively promotes wakefulness more so than sleep [69], although this hypothesis is not universally accepted. The circadian drive for wakefulness is experienced, for example, as the spontaneously enhanced alertness in the early evening, even after a sleepless

night.

Homeostatic and circadian processes do more than determine the timing of sleep. They interact to determine waking neurobehavioral alertness as expressed in fatigue and performance [70]. This is clearly seen in sustained sleep deprivation experiments (see figures 1 and 4). Consequently, for fatigue, alertness and performance (unlike body temperature) sleep and sleeplessness are not only masking factors, but also dynamic biological forces that interact with the circadian system.

The forced desynchrony protocol (e.g., [71, 72]) is a sophisticated experimental procedure for studying the interaction of the circadian and homeostatic processes [38, 44, 73]. In such a protocol, a subject stays in an isolated laboratory in which the times for sleep and waking are scheduled to deviate from the normal 24 h day (for instance, 20 h or 28 h days have been used), to such an extent that the subject's biological clock is unable to synchronize to this schedule. The subject experiences two distinct influences simultaneously: the schedule of predetermined sleep and waking times (i.e., time awake) which represents the homeostatic system, and the rhythm of the subject's unsynchronized (i.e., free-running) circadian system. Neurobehavioral variables can be recorded when the subject is in the waking periods of the schedule. By folding the data over either the free-running circadian rhythm or the imposed sleep-wake cycle, the other component can be balanced out (e.g., [74]). Thus, insight is gained into the separate effects of the circadian rhythm and the wake duration (i.e., homeostatic drive for sleep) on the recorded variables.

Not surprisingly, it has been observed in forced desynchrony studies that both the circadian and homeostatic processes influence fatigue, alertness and performance. The interaction of the two seems to be oppositional during natural diurnal wake periods (from about 07:00 hours

until 23:00 hours), such that a relatively stable level of alertness and performance can be maintained throughout the day [44]. This may explain why often in studies of alertness and performance, very little temporal variation is seen during the waking portion of the day.

Forced desynchrony studies have shown that the interaction of the homeostatic and circadian processes is complex and non-linear. Therefore, the separation of circadian and homeostatic influences on neurobehavioral variables in studies involving sleep deprivation presents a conceptual and mathematical problem [75]. It is difficult to quantify the relative importance of the two influences on neurobehavioral functions, and it is likely that their relative contributions may vary among subjects (e.g., [76]) and across different experimental conditions. In this sense the relative contribution of the circadian system may be inestimable.

Very short artificial days

The importance of taking into account sleep-wake rhythmicity when studying alertness and performance has led to the design of paradigms with very short artificial (i.e., ultradian) days, that seek to redistribute the opportunities for sleep and wakefulness across the natural 24 h day, to sample waking behavior across the circadian cycle without significantly curtailing the total amount of sleep allowed. Studies have been performed with the “90 min day” schedule [77], which alternately allows subjects to sleep for 30 min and forces them to stay awake for 60 min, and with the “7-13 min sleep-waking” schedule [5], which alternately allows subjects to sleep for 7 min and forces them to stay awake for 13 min. With respect to objective measures, studies with very short days have primarily focused on sleep propensity rather than performance, alertness and fatigue. However, subjective sleepiness scores have been

recorded in both the 90 min day schedule [77] and the 7–13 min sleep–waking schedule [78]. Surprisingly, after 24 h of 7–13 min sleep–waking cycles, the level of subjective sleepiness is elevated with respect to the initial level 24 h earlier (this does not seem to be the case in the 90 min day schedule). Thus, at least from the standpoint of subjective sleepiness, the sleep obtained across 24 h during the 7–13 min sleep–waking schedule may not have the same recovery potential as natural nighttime sleep.

Performance was assessed in one experiment employing the 7–13 min sleep–waking schedule [79]. A clear circadian rhythm emerged for the response time on a choice reaction time task. Furthermore, a movement time component was recorded, which showed a circadian rhythm as well, but also an overall gradual increase over time. This may reflect a growing homeostatic “pressure” across the artificial days. This study shows that even in paradigms with very short artificial days it is difficult to separate the circadian and homeostatic influences on neurobehavioral functions.

Another problem that may be expected to interfere with the assessment of alertness and performance in these studies, is *sleep inertia*. This is the performance impairment and the feeling of disorientation experienced immediately after waking up [80]. In the three-process model of alertness [81], which is a recent expansion of the two-process model of sleep–wake regulation, sleep inertia is the third process, called process W. Sleep inertia affects alertness and performance on every artificial day of a study with very short days. There are some indications that the other two processes of the three-process model of alertness (i.e., processes C and S) may interact with the sleep inertia to vary its impact across artificial days [82], which complicates making corrections for its effect.

Conclusion

Figure 5 schematically shows how the circadian drive for wakefulness, the homeostatic drive for sleep, and various endogenous and exogenous masking factors simultaneously affect neurobehavioral functioning. When alertness and performance are considered, masking factors cannot be regarded as mere undesirable influences that should be ignored or controlled. Rather, they are an integral part of the regulation of neurobehavioral functions. Manipulation of these endogenous and exogenous stimuli may affect the circadian and homeostatic systems via interactions which cannot yet be accurately quantified.

Place figure 5 about here.

Thorough understanding of circadian rhythmicity in neurobehavioral functions is important when either the sleep-wake rhythm is displaced, as is the case on night-work [83, 84], or when the circadian rhythm is displaced, as is the case after transmeridian flights [85]. In such situations the circadian and homeostatic systems interact to decrease alertness and performance. In fact, performance deficits and fatigue may reach dangerous levels, inducing opportunities for accidents [86, 87].

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Figure legends

Figure 1. Average (with s.e.m.) subjective alertness ratings (visual analog scale; VAS) in 24 healthy adults during 64 h of wakefulness following 8 h of sleep (black bar) from 23:30 hours until 07:30 hours. In this experiment subjects were tested on a 35 min performance and mood neurobehavioral battery every 2 h when awake. Alertness ratings are shown for two conditions: (1) ratings made just before each 35 min performance test bout (open circles); (2) ratings made directly after each 35 min performance test bout (closed circles). No graphical or statistical differences between pre-bout and post-bout alertness ratings were evident during the 16 h baseline day, or during the first 16 h of wakefulness in the sleep deprivation period. However, for most of the time from 02:00 hours on the first night awake, until 22:00 hours after 62 h awake, post-bout alertness ratings were statistically significantly ($P \leq 0.05$) lower than pre-bout ratings (times involving statistically significant differences are shown with boxes containing asterisks atop the graph). Only near the circadian peak in body temperature (i.e., from 20:00 hours until 22:00 hours) did these pre-bout versus post-bout differences disappear during sleep deprivation. Such data highlight the masking effects of ambulation, conversation, and other activity-based factors on subjective ratings of alertness, and the circadian rhythm therein, once there is a heightened pressure for sleep. This figure has not previously been published.

Figure 2. Circadian covariation of changes in subjective sleepiness as assessed by reversed visual analog scale (VAS); in cognitive performance as assessed by the digit symbol substitution task (DSST); in 10% fastest reaction times (RT) as assessed by the psychomotor vigilance task

(PVT); and in core body temperature (CBT) as assessed by means of a rectal probe. Data are the mean values from five subjects who remained awake in dim light, in bed, in a constant routine protocol, for 36 consecutive hours (a distance-weighted least-squares function was fitted to each variable). The circadian trough is evident in each variable (marked by vertical broken lines). A phase difference is also apparent, such that all three neurobehavioral variables had their average minimum between 3.0 h and 4.5 h after the time of the body temperature minimum. This phase delay in neurobehavioral functions relative to CBT has been observed in many protocols, but remains unexplained. While body temperature reflects predominantly the endogenous circadian clock, neurobehavioral functions also are affected by the homeostatic pressure for sleep, which escalates with time awake, and which may contribute to the phase delay through interaction with the circadian clock. This explanation is not universally supported by the available data, but at the very least, such data make it necessary to correct the common misconception that performance and alertness are worst at the body temperature minimum. In reality they are often worse after the time of the CBT minimum. Neurobehavioral functions generally do show the circadian decline at night as observed in CBT, but they appear to continue their decline after CBT has begun to rise, making the subsequent 2 h to 6 h period (i.e., clock time approximately 06:00 hours to 10:00 hours) a zone of maximum vulnerability to loss of alertness and performance failure. This figure has not previously been published.

Figure 3. Average cognitive throughput performance for 29 healthy adult subjects tested every 2 h from 07:30 hours until 23:30 hours each day, during a three-day period in which they were allowed up to 8 h of sleep per night (black bars). The performance task was the serial addition/subtraction test, which is a part of the Walter Reed performance assessment

battery [88]. In this task, subjects were presented with a rapid sequence of two single digits (0–9) followed by an operator (plus or minus), and they were to enter only the least-significant single digit of the algebraic sum, unless the result was negative, in which case 10 was to be added to the answer. Note the substantial learning curve (i.e., practice effect) across days, resulting in a doubling of the mean correct responses within 23 trials. This learning effect dominates the performance profile, obscuring circadian changes from 07:30 hours to 23:30 hours within any single day. Such practice effects “contaminate” nearly all tasks that involve mental operations. This figure has not previously been published.

Figure 4. Average (with s.e.m.) frequency of performance lapses (reaction times longer than 500 ms) on the 10 min psychomotor vigilance task (PVT) in 24 healthy adults during 64 h of wakefulness following 8 h of sleep (black bar) from 23:30 hours until 07:30 hours. In this experiment subjects were tested on a 35 min performance and mood neurobehavioral battery that included the PVT every 2 h when awake. As is evident in the figure, there is no circadian variation in PVT lapses during the 16 h baseline day, or during the first 16 h of wakefulness in the sleep deprivation period, because lapses are relatively rare events within this range of wakefulness duration and during this largely diurnal portion of the circadian cycle (i.e., from 07:30 hours until 23:30 hours). However, from 18 h awake (i.e., at 02:00 hours on the first sleepless night) to 62 h awake (i.e., at 22:00 hours before the third sleepless night) PVT lapses are clearly evident, indicating a substantial increase in neurobehavioral dysfunction. From 18 h to 62 h of waking, there appears to be a circadian modulation of lapsing within days, superimposed on an almost linear increase in lapses across days. This interaction makes it difficult to estimate the relative contributions of the circadian versus homeostatic influences

within and between each 24 h period. Mathematical deconvolution of the two influences, even if statistically sound, does not resolve this problem owing to potential non-linearities of the interaction. Nevertheless, it is interesting that all neurobehavioral performance and subjective variables that show circadian variation also respond to sleep loss, and vice versa, and that the combined effect of the two processes typically takes the form of a rough staircase function as seen in this figure (cf. figure 1). This figure has not previously been published.

Figure 5. Schematic representation of the speculative oppositional interplay of circadian and homeostatic drives in the regulation of alertness, performance, and related neurobehavioral functions. This representation was inspired by a number of theoretical conceptualizations, but it does not necessarily reflect their authors' original intentions. These include the two-process model of sleep-wake regulation [67] and the opponent-process model of sleep-wake regulation [69]; the two- and three-process models of the endogenous neurobiological regulation of subjective sleepiness [70, 81] and of performance and alertness [38, 89]; and by a study of the effects of postural, environmental, cognitive, and social stimulation (masking) on neurobehavioral functions at different circadian phases during sleep deprivation [90]. The schematic is necessarily simplified (e.g., an additional factor, *sleep inertia*, is subsumed under the homeostatic drive for sleep). As represented in the figure, the *homeostatic* drive for sleep, which involves continuous time awake and loss of sleep (or disruption of the recovery function of sleep), decreases waking neurobehavioral performance and alertness (and increases fatigue and subjective sleepiness) as it accumulates over time. Unlike the circadian component, which is limited by its amplitude, the homeostatic drive for sleep can accumulate far beyond the levels typically encountered in a 24 h day (illustrated by the increasing density of downward

arrows). The neurobiology of the cumulative homeostatic pressure is unknown. In opposition to this downward influence on performance and alertness is the endogenous *circadian* rhythmicity of the biological clock, which through its promotion of wakefulness, modulates the enhancement of performance and alertness. Although the neurobiology of the biological clock is increasingly elucidated, the ways in which it controls the drive for wakefulness and enhances alertness are still unknown. The improvement in waking neurobehavioral functions by the circadian drive is an oscillatory output with some phases involving robust opposition to the homeostatic drive, although the phase of the lowest circadian opposition may involve a complete absence of circadian drive for wakefulness. Critical modulators of neurobehavioral functions other than the sleep and circadian drives are subsumed in the schematic under the broad categories of *endogenous* and *exogenous* stimulation. Although common in the real world, these factors are considered masking factors in most laboratory experiments. They can include endogenous (e.g., anxiety) or exogenous (e.g., environmental cues) wake-promoting processes that oppose the homeostatic drive for sleep. Alternatively, they can include endogenous (e.g., narcolepsy) or exogenous (e.g., rhythmic motion) sleep-promoting processes that oppose the circadian drive for wakefulness either directly, or indirectly by exposing the previously countered sleep drive [4, 91]. The neurobiological underpinnings of these exogenous and endogenous processes are undoubtedly diverse, and few of their interactions with the circadian and homeostatic systems have been studied systematically. This figure has not previously been published.