CHAPTER SEVEN

Circadian Rhythms, Sleep Deprivation, and Human Performance

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Abstract

Much of the current science on, and mathematical modeling of, dynamic changes in human performance within and between days is dominated by the two-process model of sleep–wake regulation, which posits a neurobiological drive for sleep that varies homeostatically (increasing as a saturating exponential during wakefulness and decreasing in a like manner during sleep), and a circadian process that neurobiologically modulates both the homeostatic drive for sleep and waking alertness and performance.

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Endogenous circadian rhythms in neurobehavioral functions, including physiological alertness and cognitive performance, have been demonstrated using special laboratory protocols that reveal the interaction of the biological clock with the sleep homeostatic drive. Individual differences in circadian rhythms and genetic and other components underlying such differences also influence waking neurobehavioral functions. Both acute total sleep deprivation and chronic sleep restriction increase homeostatic sleep drive and degrade waking neurobehavioral functions as reflected in sleepiness, attention, cognitive speed, and memory. Recent evidence indicating a high degree of stability in neurobehavioral responses to sleep loss suggests that these trait-like individual differences are phenotypic and likely involve genetic components, including circadian genes. Recent experiments have revealed both sleep homeostatic and circadian effects on brain metabolism and neural activation. Investigation of the neural and genetic mechanisms underlying the dynamically complex interaction between sleep homeostasis and circadian systems is beginning. A key goal of this work is to identify biomarkers that accurately predict human performance in situations in which the circadian and sleep homeostatic systems are perturbed.

1. INTRODUCTION

Sleep is a ubiquitous biological imperative that appears to be evolutionarily conserved across species.[1] Sleep of sufficient duration, continuity, and intensity (depth) without circadian disruption is necessary to promote high levels of attention and cognitive performance during the wake period, and to prevent physiological changes that may predispose individuals to adverse health outcomes.[2] The evidence linking habitually short sleep or circadian desynchrony to conditions such as weight gain,[3,4] obesity,[5] diabetes,[6] and hypertension,[7] as well as to increased mortality,[8] has accumulated over the past decade. These negative cognitive and health consequences of sleep restriction are provocative, given that current representative surveys indicate 35–40% of the adult US population report sleeping less than 7 h on weekday nights,[9] which has been experimentally demonstrated to result in cumulative deficits in behavioral alertness and vigilant attention.[10]

A lifestyle of chronic partial sleep loss that is often paired with chronic stimulant use (e.g., caffeine)[11] may at least in part be explained by the fact that humans frequently alter the timing and duration of sleep in exchange for other activities. This altered behavior appears to be prevalent in current industrialized societies, where the biological imperative to sleep adequately often opposes the cultural imperative to spend more time awake.[12] Sleep may be perceived as a flexible commodity that is traded for other activities

considered more pressing or of greater value.[13] Analyses of the American Time Use Survey (ATUS) revealed that paid work time and commuting to and from work were the two waking activities most often exchanged for sleep time.[14] Sleep time was lowest in the 45- to 54-year-old respondents, shorter in men than in women, and shorter on weekdays compared to weekends. An ATUS analysis on waking activities in the 2-h period before retiring in the evening and after waking up in the morning showed that watching TV was the dominant (>50%) activity in the 2 h before retiring.[15] Long work hours were associated with progressively earlier wake-up times in the morning, while long-hour workers, short-hour workers, and those who did not work did not differ in the times when they retired at night.[15] We speculate that some of this sleep-restriction behavior may be explained by respondents with a late evening circadian phase preference, who awaken early by alarm clock to commute for paid work. These individuals cannot easily advance their sleep onset, but they can use an alarm clock to advance their sleep offset (for commuting and paid work), resulting in a restricted sleep period. This misalignment of biological and social time has been termed "social jet lag" by Roenneberg and colleagues.[16] Individuals with a late circadian preference thus often engage in chronic sleep restriction during the work week, and try to pay off their sleep debt on the weekend. Furthermore, shift work affects sleep and alertness of approximately one out of five working Americans, with 15% of full-time salaried workers usually working shifts that include nights.[17] Shift work includes working evenings, nights, or rotating shifts and is often associated with shorter-than-normal and disrupted sleep periods at an adverse circadian phase.[18] The International Agency for Research on Cancer concluded in 2007 that shift work involving circadian disruption is probably carcinogenic to humans.[17,19]

2. SLEEP–WAKE AND CIRCADIAN REGULATION: TWO-PROCESS MODEL

The two-process model of sleep–wake regulation has been applied to the temporal profiles of sleep[20,21] and daytime vigilance.[22] The model consists of a homeostatic process (S) and a circadian process (C), which combine to determine the timing of sleep onset and offset. The homeostatic process represents the drive for sleep that increases as a saturating exponential during wakefulness (as can be observed when wakefulness is maintained beyond habitual bedtime into the night and subsequent day) and decreases as a

saturating exponential during sleep (which represents recuperation obtained from sleep). When the homeostat increases above a certain threshold, sleep is triggered; when it decreases below a different threshold, wakefulness occurs. The circadian process represents daily oscillatory modulation of these threshold levels. It has been suggested that the circadian system actively promotes wakefulness more than sleep.[23] The circadian drive for wakefulness may be manifested as spontaneously enhanced alertness and better cognitive performance in the early evening after one night or multiple nights without sleep[24,25] (Figs. 7.1 and 7.2).

The endogenous circadian regulating system (i.e., biological clock) that modulates the timing of both sleep and wakefulness is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. Beyond gating the timing of sleep onset and offset, the SCN modulates waking behavior in a circadian manner, as reflected in subjective and physiological sleepiness, behavioral alertness, and a number of fundamental cognitive functions, including vigilant attention, psychomotor and perceptual cognitive speed, and working memory.

Alertness and performance, sleep and sleeplessness are neurobehavioral outputs that involve dynamic circadian variation. Recent forced desynchrony protocols, which serve to experimentally reveal the variance in neurobehavioral functions attributable primarily to endogenous circadian control and the variance attributable primarily to the sleep homeostatic drive, have revealed that circadian dynamics can expose large neurobehavioral vulnerability during chronic sleep restriction.[26,27] These studies demonstrated that sleep restriction induced decreased vigilant attention, as measured by the Psychomotor Vigilance Test (PVT),[25] most prominently during circadian night, even with short prior wake duration. Another study found that time of day modulated the effects of chronic sleep restriction, whereby the build-up rate of cumulative neurobehavioral deficits across days was largest at 0800 h and became progressively smaller across the hours of the day, especially between 1600 and 2000 h, indicating a late afternoon/early evening period of relatively protected alertness.[28]

Thus, while the two-process model has been very successful in explaining changes in neurobehavioral performance in acute total sleep deprivation paradigms, it fails to adequately predict the escalating declines in vigilant attention observed under chronic sleep-restriction conditions.

The two-process model has proved to be most useful for generating mathematical predictions of the dynamics of human alertness and performance under varying conditions of sleep loss and circadian misalignment.[29]

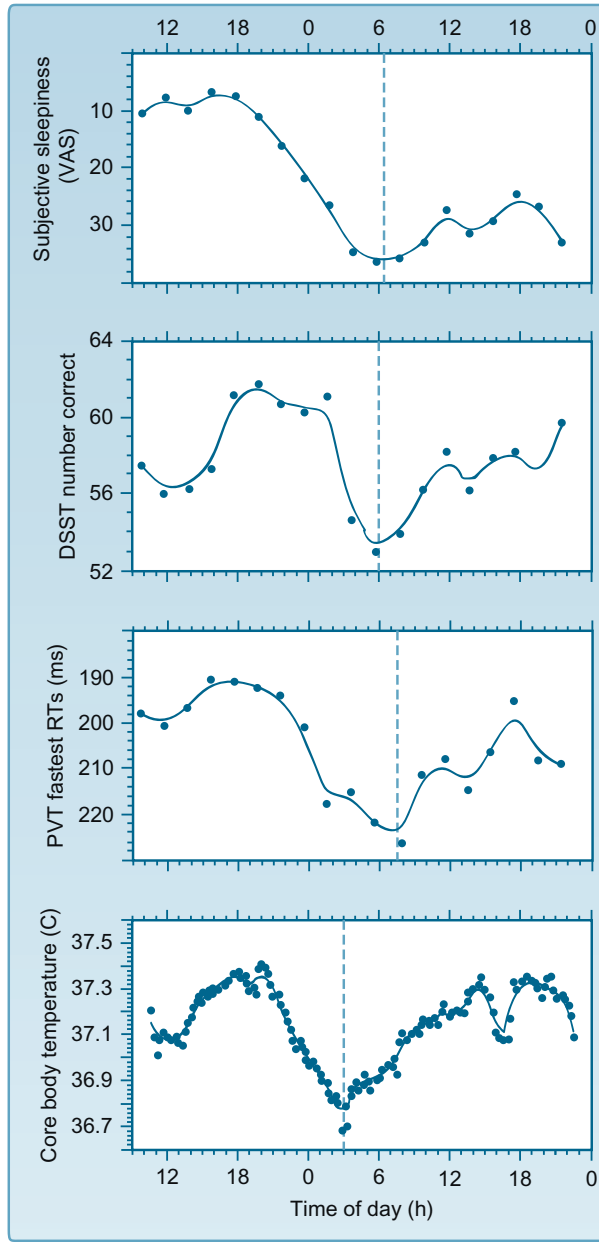

Figure 7.1 See legend on next page

When these mathematical models are compared to emerging experimental data on performance relative to sleep–wake dynamics, they often reveal new deficiencies in the two-process model.[30] An excellent example of this need to continually improve the predictions of the two-process model can be found in a mathematical modeling paper by McCauley and colleagues,[31] who showed that the two-process model belongs to a broader class of models formulated in terms of coupled nonhomogeneous first-order ordinary differential equations. Their new model includes an additional component modulating the homeostatic process across days and weeks, and better reflects the neurobehavioral changes observed under both acute total and chronic partial sleep loss than the original two-process model. The authors speculate that adenosine receptor upregulation (wakefulness) and downregulation (sleep) constitute the underlying neurobiological mechanism. Importantly, the model predicts a critical amount of daily wake duration of 20.2 h. If daily wake duration is above ca. 15.8 h[32] but below 20.2 h (corresponding to a total sleep time of 3.8–8.2 h), the model, over a period of weeks, converges to an asymptotically stable equilibrium (i.e., performance deficits will stabilize at a certain level). If daily wake duration is above 20.2 h, the model diverges and, similar to acute total sleep deprivation, performance impairments escalate.[31] The model of McCauley *et al.*[31] also

Figure 7.1 Circadian variation across a 40-h period of wakefulness in measures of subjective sleepiness as assessed by visual analogue scale (VAS, note reversed scale direction); in cognitive performance speed as assessed by the digit symbol substitution task (DSST); in psychomotor speed as reflected in the 10% fastest reaction times (RT) assessed by the Psychomotor Vigilance Test (PVT); and in core body temperature (CBT) as assessed by a rectal thermistor. Data shown are the mean values from five subjects who remained awake in dim light, in bed, in a constant routine protocol, for 36 h consecutively (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 and 4.5 h after the time of the body temperature minimum. This phase delay in neurobehavioral functions relative to CBT has been consistently observed. Although body temperature reflects predominantly the endogenous circadian clock, neurobehavioral functions are also 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. Neurobehavioral functions usually show a circadian decline at night as is observed in CBT, but they continue their decline after CBT begins to rise, making the subsequent 2–6 h period (clock time approximately 0600–1000 h) a zone of maximum vulnerability to loss of alertness and to performance failure.*Reprinted with permission from Ref. 256.*

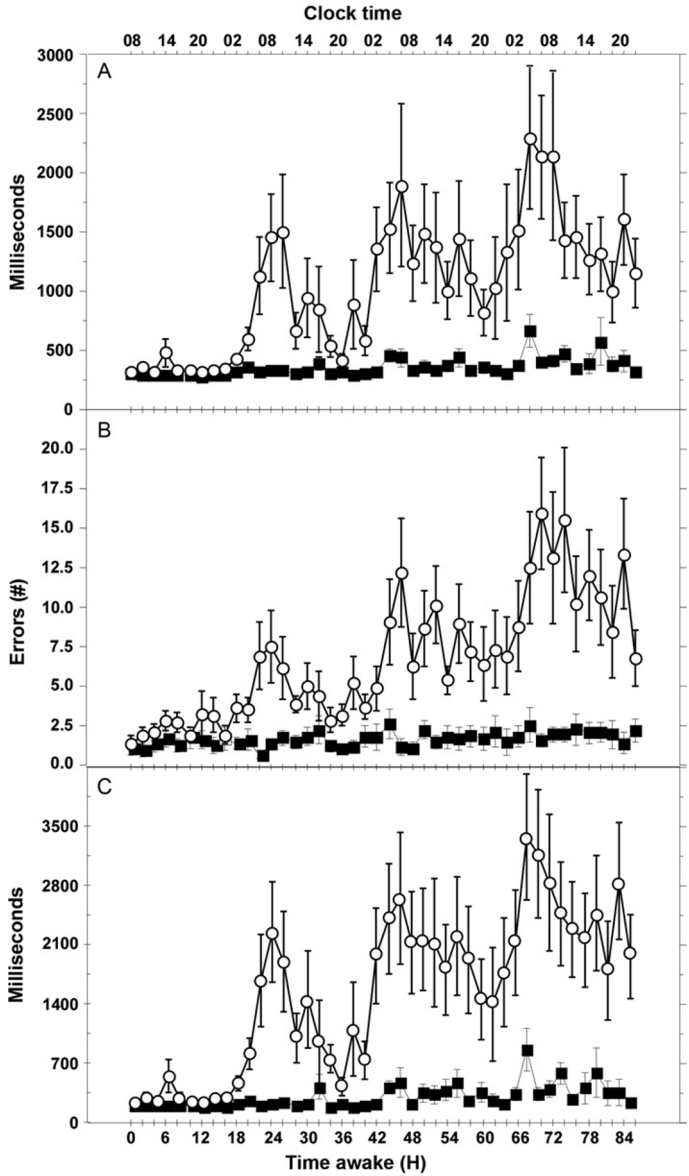

Figure 7.2 See legend on next page

predicts that a single night of recovery sleep is inadequate to recover from a prolonged period of sleep restriction, a finding we recently experimentally confirmed.[33] It is recognized that further model development is needed to integrate more comprehensive mathematical models of the circadian component and to account for sleep inertia and trait-like individual differences in vulnerability to sleep loss.[31]

3. CIRCADIAN RHYTHMS OF PERFORMANCE

3.1. Subjective measures of sleepiness and alertness

A variety of subjective measures of sleepiness and alertness reflect circadian variation, as long as the scale requests ratings about the near immediate state of the subject. These include visual analogue scales,[34] Likert-type rating scales such as the Stanford Sleepiness Scale[35] and the Karolinska Sleepiness Scale,[36] and certain fatigue-related subscales of standard adjective checklists such as the Activation–Deactivation Adjective Check List[37] and Profile of Mood States.[38] Despite structural differences among these scales, all self-reports of sleepiness are highly intercorrelated and because they are relative psychometrics, they are subject to a number of sources of variance, including different uses of the scale response range by different subjects. The effects of cognitive performance testing on subsequent posttest subjective alertness ratings are evident only when sleep loss has commenced and this effect is modulated by circadian variation.[28]

3.2. Objective measures of cognitive performance

Many studies rely on objective performance measures to track the temporal dynamics of endogenous circadian rhythmicity. Circadian variation in

Figure 7.2 Psychomotor Vigilance Test (PVT) performance parameters of healthy adults during an 88 h period of limited to no sleep in the laboratory. The open circles represent 13 subjects undergoing 88 h of total sleep deprivation, and the filled squares represent 15 control subjects given a 2-h time in bed nap opportunity once every 12 h (0245–0445 h and 1445–1645 h) throughout the 88 h period (nap times are not shown in the figure). Graph A: mean (SEM) PVT reaction times (RT), which as RTs > 500 ms are frank errors of omission and referred to as lapses of attention (i.e., responding too slowly). Graph B: mean (SEM) PVT errors of commission, which result from premature responses and reflect impulsiveness (i.e., responding too fast). Graph C: mean (SEM) of PVT RT standard deviations for each test bout, reflecting the magnitude of interindividual differences in performance. The subjects who underwent 88 h without sleep showed clear circadian variation in both lapses of attention (A) and premature responses (B), as well as interindividual differences in these effects (C). *Figure adapted and modified with permission from Ref. 24.*

performance is most evident when sleep loss is present, and sleep loss has its largest effects on attention, working memory, and cognitive throughput.[39] Examples of such cognitive performance measures that have historically been reported to display circadian variation include the following: search-and-detection tasks[40] and simple and choice reaction time tasks,[41] sorting,[42] logical reasoning,[43] memory access,[44] and real-world tasks such as meter reading accuracy[45] and school performance.[46] Typically, response speed and accuracy to a series of repetitive stimuli are analyzed, although the sensitivity of the performance metric used to track circadian variation depends on whether the task is work-paced versus subject-paced, on speed versus accuracy trade-offs in performance metrics,[47] on the rate and number of responses acquired during the task, on whether the task metrics reflect performance variability or mean performance, and on the overall technical precision of the measurement. Even short-duration, work-paced tasks that precisely measure variability in performance can be used to demonstrate circadian variation.[48] It is likely that the modulatory effects the circadian system has on speed and accuracy make many tasks sensitive to process C, more so than any unique aspect of task demand.

Earlier studies concluded that different tasks[49,50] and different task outcomes[51,52] may yield distinct peak phases of circadian rhythmicity, suggesting that many distinct circadian rhythms utilizing different clock mechanisms exist.[53,54] Under strictly controlled laboratory conditions, most intertask differences in circadian variation disappear.[55,56] As illustrated in Fig. 7.1, under controlled sleep deprivation conditions, the circadian rhythms of neurobehavioral performance variables covary with each other and with subjective sleepiness. Importantly, these rhythms mimic the circadian profile of core body temperature, one conventional marker of the biological clock.[57,58] Under entrained conditions, higher and lower core body temperature values typically correspond to good and poor performance, respectively.[56,59,60]

3.3. Masking factors

Subjective measures of sleepiness and alertness are vulnerable to numerous confounding influences that can "mask" their circadian rhythmicity. Masking refers to the evoked effects of noncircadian factors on 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 alter or obscure a circadian rhythm, or create the appearance of a circadian rhythm. Masking factors specifically

affecting sleepiness and alertness include the following demand characteristics of the experiment,[61] distractions by environmental stimuli and noise,[62] boredom and motivational factors,[63–65] stress,[66] food intake,[67,68] posture and activity,[69,70] ambient temperature,[64] lighting conditions,[71,72] and stimulant drug intake (e.g., caffeine, modafinil, amphetamine).[73–75]

Physical, mental, and social activities can represent masking factors that interact with endogenous circadian rhythms in neurobehavioral functions. The effects of performing cognitive tests on subjective estimates of alertness are apparent at certain circadian phases during sleep deprivation. Subjects report feeling less alert after they are challenged to perform. Thus, prior activity can influence subjective estimates, and can interact with circadian effects if not properly controlled when measuring the rhythmicity of subjective states.

Sleep and sleep loss can also be considered masking factors when measuring circadian rhythmicity in certain neurobehavioral variables. Therefore, neurobehavioral measures reflect to varying degrees a combination of endogenous circadian rhythmicity, sleep homeostatic drive, and masking effects interacting to produce behavioral outcomes.

4. PROTOCOLS TO ASSESS CIRCADIAN VARIATION IN NEUROBEHAVIORAL FUNCTIONS

Considerable research has been devoted to unmasking circadian rhythms, that is, eliminating sources of extraneous variance to expose the endogenous circadian rhythms of variables of interest, including alertness and cognitive performance. Two such experimental approaches are the use of a constant routine protocol and the use of a forced desynchrony protocol.

4.1. Constant routine

The constant routine procedure[76] is 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 variety of physiologic and neurobehavioral variables can be recorded without biases (Fig. 7.1). Indeed, the circadian rhythm of body temperature is believed to be largely free of masking effects when derived under a constant routine.

However, when neurobehavioral variables are considered, sleep deprivation and the stimuli used to sustain wakefulness can constitute masking

factors. In constant routine experiments, these masking effects are evident in subjective measures of sleepiness and alertness.[57,77] Figure 7.1 shows the somewhat reduced values for subjective alertness as well as cognitive and psychomotor performance after 30 h awake in a constant routine, compared with the values of these variables 24 h earlier (i.e., at the same circadian phase but without sleep deprivation).

Recently, the constant routine protocol has been used to examine metabolites in saliva and plasma at different times of day to identify those that are under circadian control and are independent of sleep.[78,79] Remarkably, one study found that metabolites from blood taken every 2 h, which were used to form a circadian timetable, could subsequently be used to predict internal time within a 3-h interval using only two blood samples.[80] More recently, a constant routine was used to examine the effects of chronic sleep restriction on circadian rhythmicity and amplitude of genes that were upregulated or downregulated using a transcriptome analysis, highlighting the critical interaction between sleep homeostasis and circadian rhythms at the mRNA level.[81]

A progressive change associated with the time spent awake is typically superimposed on the circadian rhythm of neurobehavioral variables.[82,83] 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 increase, and although the circadian process can be exposed,[84] it is overlaid on a continuing (nearly linear) change reflecting increasing homeostatic pressure for sleep.[85] This is illustrated in Fig. 7.2 for PVT performance lapses—perhaps the most sensitive waking measure of homeostatic sleep drive and circadian phase, and the least masked by aptitude and learning.[25,86] It is noteworthy that decreased alertness during the circadian trough is associated with increased intra-individual variability in performance. This is evidenced by intermittent lapsing (reaction times >500 ms)[87] which reflects wake state instability.[24,25] The wake state instability hypothesis posits that sleep-initiating mechanisms may interfere with wakefulness, making sustained performance unstable and dependent on compensatory mechanisms.[25]

4.2. Forced desynchrony

The forced desynchrony protocol[88,89] conducted in temporally and environmentally isolated conditions, is an experimental procedure particularly suitable for studying the interaction of the circadian and homeostatic processes.[55,90,91] In this protocol, a subject's imposed timing and duration of

wake and sleep (typically maintained in a 2:1 ratio) deviate from the normal 24-h day (e.g., 20- or 28-h days), such that the subject's biological clock is unable to entrain to this schedule. The subject experiences two distinct influences simultaneously—the schedule of predetermined sleep and waking times representing the homeostatic system and the rhythm of the subject's unsynchronized (i.e., free-running) circadian system. Neurobehavioral functions are assayed during the waking periods. By folding the data over either the free-running circadian rhythm or the imposed sleep–wake cycle, the other component can be balanced out. Thus, the separate effects of circadian rhythms and wake duration (i.e., homeostatic drive for sleep) on neurobehavioral variables can be assessed.

Forced desynchrony studies have found that both the circadian and homeostatic processes influence sleepiness and performance.[26,27] The interaction of the two systems is oppositional during diurnal wake periods (from approximately 0700 h until 2300 h), such that a relatively stable level of alertness and performance can be maintained throughout the day.[89,90] This explains why in many studies of alertness and performance, very little temporal variation is observed during the waking portion of a normal day, especially when there is no sleep deprivation[24] (Fig. 7.2).

The interaction of the homeostatic and circadian processes is believed to be nonlinear (i.e., nonadditive).[90,92] Therefore, the separation of circadian and homeostatic influences on neurobehavioral variables presents a conceptual and mathematical challenge, and it is difficult, if not impossible, to quantify the relative importance of the two influences on neurobehavioral functions. Moreover, their relative contributions may vary across different experimental conditions[55,90] and among subjects.[93]

5. INTERINDIVIDUAL VARIABILITY IN CIRCADIAN RHYTHMS

Healthy adults show interindividual differences in the free-running circadian period (tau),[94–98] which shows robust stability within individuals.[97] Subjects also demonstrate interindividual differences in circadian amplitude[58,99] and circadian phase[57,58,95,99] which are in part due to genetic influences.[99] There are several standardized methods for assessing interindividual differences in circadian rhythms. One newer method, using molecular techniques, can determine individual differences in tau, amplitude, and phase-resetting, which relate to diurnal phase preference, using cultured human

fibroblasts from skin biopsies or blood samples.[100–102] While these *in vitro* skin fibroblasts can determine circadian rhythms and period, they do not necessarily correlate with *in vivo* physiological rhythms,[97] limiting the validity and utility of this technique. Standard physiological estimates of circadian phase include the dim light melatonin onset[103] and core body temperature minimum.[57,58] These methods are important for characterizing interindividual variation in circadian rhythmicity.

5.1. Chronotype (morningness–eveningness)

Chronotype or morningness–eveningness (i.e., the tendency to be an early "lark" or a late "owl") is perhaps the most frequently measured interindividual variation in circadian rhythmicity. Morning- and evening-type individuals differ endogenously in the circadian phase of their biological clocks.[57,58] Self-report questionnaires, such as the Horne–Östberg morningness–eveningness questionnaire[104] and its variants,[105] and the Munich ChronoType Questionnaire,[106,107] differentiate timing of activities on workdays versus free days. They are the most commonly utilized measures of circadian phase preference, because of their convenience and cost effectiveness.

Age affects morningness–eveningness as shown in laboratory studies[108] and more naturalistic population-based settings.[107,109] In addition, gender influences morningness–eveningness with women showing a greater skew toward morningness than men.[107,110–112] Women also have been reported to have a shorter average intrinsic circadian period than men,[113] though not consistently,[114] and blacks have been reported to have a shorter average intrinsic circadian period than whites.[114] These differences in circadian phase preference (and possibly in circadian period) appear to be enduring traits, with a significant genetic basis across various diverse populations.[115–120] As such, chronotype is a phenotypic aspect of circadian rhythmicity in humans.[121]

In line with the two-process model, the relationship of chronotype to the regulation of sleep and neurobehavioral responses to sleep deprivation has been investigated in laboratory studies. Chronotypes showed differences in homeostatic sleep regulation[122–124] and in homeostatic response to sleep fragmentation.[125] Moreover, chronotypes showed differences in neurobehavioral responses to sleep fragmentation[126] and to total sleep deprivation,[127] and to risk-taking propensity at baseline and following total sleep deprivation.[128]

5.2. Genetics of individual differences in chronotype and circadian rhythms

Morningness–eveningness is estimated to be about 50% heritable.[129] The genetic basis of morningness–eveningness in the general population has been investigated by targeting several core circadian genes, producing inconsistent results.[130] For example, the 3111C allele of the *CLOCK* gene 5′-UTR region has been associated with eveningness and delayed sleep timing in some studies[131–133] but not others.[98,134–138] Similarly, the variable number tandem repeat (VNTR) polymorphism in *PERIOD3* (*PER3*), another core clock gene, has been linked to diurnal preference, but not consistently,[135,139–148] thereby underscoring the need for further investigation on this topic. Both the 111G polymorphism in the 5′-untranslated region of *PERIOD2* (*PER2*) and the T2434C polymorphism of *PERIOD1* have been associated with morning preference[149,150] though not consistently.[134] Since morningness–eveningness represents a continuum, it is likely this trait is polygenic, influenced by several genes, each contributing to the determination of circadian phase preference. Thus, further studies investigating other clock genes, as well as replication of the *PER* and *CLOCK* findings, are needed to establish precisely the molecular components of behavioral circadian phase preference.

Interindividual differences in morningness–eveningness are believed to manifest into extreme cases classified as primary circadian rhythm sleep disorders (CRSDs), with altered phase relationships of the biological clock to the light–dark cycle, including alterations in sleep timing.[151,152] Thus, extreme eveningness is thought to result in CRSD, delayed sleep phase type (usually referred to as a disorder and abbreviated as DSPD[152]), while extreme morningness can manifest as CRSD, advanced sleep phase type (usually referred to as a disorder and abbreviated as ASPD).[151,152] The extent to which these phase-displacement disorders reflect differences in endogenous circadian period, amplitude, coupling, entrainment, or other aspects of clock neurobiology has been the focus of recent research.

The genetic basis of DSPD and ASPD related to phenotypic chronotype has been investigated in recent years, both demonstrating links to core clock genes.[130,153,154] DSPD, the most common CRSD in the general population, is characterized by an inability to fall asleep at the desired and "normal" time of day; the average onset of sleep in DSPD occurs in the early morning (0300–0600 h), and the average wake-up time occurs in the late morning to early afternoon (1100–1400 h).[152] DSPD also may be characterized by a longer than normal tau (e.g., $\geq$25 h).[155] The VNTR polymorphism in *PER3* is associated with DSPD in large sample studies,[139,140,142] and the

3111C allele of the *CLOCK* gene 5′-UTR region also has been related to DSPD.[131] In addition, a specific haplotype of *PER3*, which includes the polymorphism G647, is associated positively with DSPD,[142] while the N408 allele of casein kinase I epsilon protects against DSPD in a Japanese population[156] but not in a Brazilian population.[157]

ASPD is a rarer disorder than DSPD and is characterized by 3- to 4-h advanced sleep onsets and wake times relative to desired, normal times.[152,158] It may be associated with a shorter-than-normal tau (e.g., <24 h).[159] In one study, ASPD was shown to be associated with a mutation in *PER2*,[160] although a later study failed to replicate this finding.[161] Another report implicated mutations in casein kinase I delta in ASPD.[162] Future studies on additional core clock genes are needed to determine other mutations that may underlie this disorder.

Morningness–eveningness and differences in circadian phase preference are reflected in the diurnal time course of neurobehavioral variables[163]—some people perform consistently better in the morning, whereas others are more alert and perform better in the evening.

How genetic variants underlying morningness–eveningness and chronotype disorders affect performance and alertness under normal and sleep-deprived conditions remains an emerging and important field of investigation. Two studies have shown that the longer, 5-repeat allele of the VNTR polymorphism in *PER3*, a clock gene linked to diurnal preference and DSPD, may be associated with higher sleep propensity both at baseline and after total sleep deprivation, and worse cognitive performance following sleep loss.[143,144] However, a study from our laboratory found that this polymorphism related to individual differences in sleep homeostatic responses, but not performance responses to chronic sleep restriction.[148] The role of other core clock gene polymorphisms in response to total sleep deprivation or chronic sleep restriction remains unknown.

A number of core clock genes have been associated with interindividual differences in diurnal preference or its extreme variants. This area of research has promising implications for objectively detecting differential vulnerability to circadian disorders and lifestyles that adversely affect alertness, performance and sleep duration, and homeostasis.

6. SLEEP DEPRIVATION AND PERFORMANCE

Sleep deprivation induces a variety of physiological and neurobehavioral changes.[164] Both objective and subjective measures of sleep

propensity increase with sleep deprivation. Sleep deprivation affects a wide range of cognitive domains (including attention, working memory, abstraction, and decision making) and results in decreases in both the encoding of new information and memory consolidation.[165] Vigilant attention performance and psychomotor speed, as assessed with the PVT, are affected early and progressively more severely by sleep deprivation.[86,166] Although sustained attention seems a prerequisite for high levels of performance on more complex cognitive tasks, several studies have shown that the latter are less affected by sleep loss than attention, probably because they are more challenging and engaging than sustained attention tasks that unmask fatigue by their limited evocation of additional neural processing areas.[39,167] In addition, some of the differences among tasks in sensitivity to sleep deprivation may be explained by practice effects confounding the effects of sleep deprivation on more complex tasks. At the same time, the ability of stimulants to counteract the effects of sleep deprivation seems to depend on the cognitive domain studied.[168]

The neurobehavioral effects of chronic sleep restriction are less severe than those observed after acute total sleep deprivation, but the former can reach levels of deficit equivalent to total sleep loss when the sleep restriction is severe enough (i.e., the consecutive days of restricted sleep continue long enough).[10,32] Chronic sleep-restriction experiments suggest that the neurobiology underlying the neurobehavioral deficits can continue to undergo long-term changes. This is supported by a study investigating recovery after a period of chronic sleep restriction that suggests a single recovery night of up to 10 h time in bed is insufficient for some behavioral functions to return to prerestriction levels.[33] Evidence of longer time constants in homeostatic sleep pressure manifesting in waking neurobehavioral functions was reported by Rupp *et al.*[169] who varied the amount of baseline nightly sleep prior to chronic sleep restriction and found that it affected both the rate at which alertness was degraded and the rate at which deficits were reversed by repeated nights of recovery sleep.

6.1. Phenotypic and genotypic differences in response to sleep deprivation

We have repeatedly demonstrated that there are large and highly replicable, trait-like individual differences in the magnitude of fatigue, sleepiness, sleep homeostatic, and cognitive performance vulnerability to acute total sleep deprivation[170,171] and to chronic sleep restriction.[32,148,172,173] Some individuals are highly vulnerable to neurobehavioral performance deficits when

sleep deprived, others demonstrate remarkable levels of neurobehavioral resistance to sleep loss, and others show intermediate responses.[171,174] Thus far, studies from our laboratory and others indicate these phenotypic responses occur as a normal distribution,[170,175] which suggests the phenotype, like chronotype, may be polygenetic.

It remains unclear, however, whether the same individuals vulnerable to the adverse neurobehavioral effects of chronic sleep restriction are also vulnerable to acute total sleep deprivation. Some studies have reported differences in behavioral, sleep homeostatic and/or physiological responses to both types of deprivation.[32,176,177] Moreover, only a few experiments have systematically examined the same subjects in both types of deprivation.[167,175,178–180] These studies reported inconsistent results, likely due to small sample sizes, different populations, varying doses of sleep restriction, and different outcome measures.

The reasons for differential neurobehavioral vulnerabilities to sleep loss are unknown, and thus far have not been accounted for by demographic factors, IQ, or sleep need. Moreover, psychometric scales have not reliably identified cognitively vulnerable individuals.[181] The stable, trait-like interindividual differences observed in response to acute total sleep deprivation—with intraclass correlation coefficients accounting for 50–90% of the variance in neurobehavioral measures[170,171]—point to underlying genetic components. In support of this statement, a recent study by Kuna *et al.*[182] conducted in monozygotic and dizygotic twin pairs, found substantial differences in individual neurobehavioral responses to total sleep deprivation—56.2% of the total variance in the monozygotic twins was due to variance between pairs whereas only 14.5% of the total variance in dizygotic twins was due to variance between pairs (Fig. 7.3), indicating that the response to acute total sleep deprivation is a highly stable, genetically determined trait. Indeed, data from unrelated individuals further indicate that common genetic polymorphisms involved in sleep–wake, circadian, and cognitive regulation may underlie these large interindividual differences in neurobehavioral vulnerability to sleep deprivation in healthy adults.[164,181,183]

Because of reported differences in behavioral, sleep homeostatic, and physiological responses to chronic sleep restriction and acute total sleep deprivation, specific candidate genes may play different roles in the degree of vulnerability and/or resilience to the neurobehavioral and homeostatic effects of acute total sleep deprivation and chronic sleep restriction. Two examples—one from a genetic variation involved in circadian regulation and one from a genetic variation involved in a cognitive regulation—

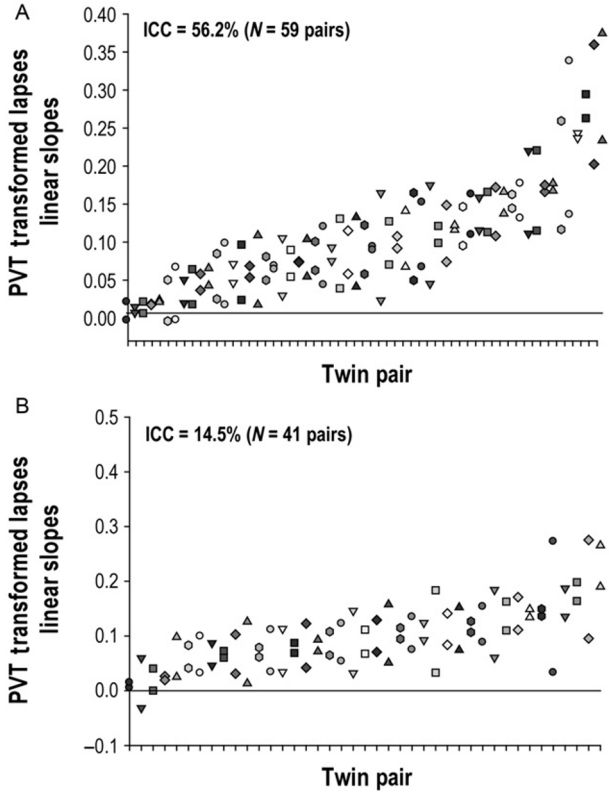

Figure 7.3 The individual linear slopes of the change in Psychomotor Vigilance Task (PVT) transformed lapses during 38 h of total sleep deprivation in monozygotic (MZ; A) and dizygotic (DZ; B) twin pairs. Data for each MZ and DZ twin pair are plotted together on the abscissa. In each panel, the pairs are ordered by the magnitude of their impairment (averaged over each pair), with the most resistant twin pair on the left and the most vulnerable twin pair on the right. The panels reveal substantial differences in individual responses to sleep deprivation. The intraclass correlation (ICC) revealed greater similarity within MZ twin pairs than within DZ twin pairs. There was 56.2% of the total variance in the MZ twins due to variance between pairs whereas only 14.5% of the total variance in DZ twins was due to variance between pairs. *Reprinted with permission from Ref. 182.*

illustrate this point. As mentioned previously, the *PER3* VNTR polymorphism has been associated with individual differences in sleep homeostatic and executive performance responses to acute total sleep deprivation.[143,144] We showed that this polymorphism related to individual differences in sleep homeostatic responses, but not cognitive performance responses to chronic sleep restriction.[148] By contrast, two recent studies,[167,184] which used

different sleep-restriction paradigms than that of Goel *et al.*,[148] claimed that the *PER3* VNTR polymorphism was related to individual differences in neurobehavioral responses to chronic sleep restriction. Notably, one of these[184] failed to include subjects from the critical *PER3*$^{5/5}$ putatively vulnerable genotype, and thus its findings must be interpreted cautiously and replicated in the appropriately inclusive genotypes. As another example, we found that the *catechol-O-methyltransferase* Val158Met polymorphism predicted individual differences in sleep homeostatic responses to chronic sleep restriction,[173] but such prediction has not been shown to acute total sleep deprivation.[185] Clearly, more studies are warranted to investigate potential genotypic markers of phenotypic vulnerability to sleep loss and the differential role they might play in response to different types of sleep loss.

6.2. Neuroimaging of sleep deprivation and circadian variations in brain metabolism and neural activity

With few exceptions, the influences of sleep deprivation and circadian variations on brain metabolism and neural activity have been studied separately in the past two decades using various neuroimaging methods, particularly positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

PET studies of sleep deprivation have consistently reported significant reductions in metabolic rates in the thalamic, parietal, and prefrontal regions after sleep loss, which correlated with declines of cognitive performance and alertness.[186–189] An early PET study examined the effects of time of day (a surrogate for circadian phase) on the cerebral metabolic rate of glucose and observed a trend toward increased whole brain glucose metabolism from the morning to the afternoon scans.[190] A more recent PET study found increased relative glucose metabolism in the brainstem and hypothalamic arousal systems and decreased relative metabolism in the posterior cortical regions during evening wakefulness compared with morning wakefulness.[191] Moreover, variations in regional brain glucose metabolism have been reported to differ across morning and evening scans in depressed and healthy adult subjects.[192] New PET studies on neurotransmitter receptors have shown downregulation of striatal dopamine receptors[193] but increases in cerebral serotonin receptor binding with sleep loss,[194] which may reflect a complex adaptive brain response to sleep deprivation. However, due to its invasiveness and the rapid decay of radioactive tracers, further

utility of PET in imaging human brain metabolism variations associated with sleep deprivation and time-of-day effects is limited.

The vast majority of sleep deprivation and time-of-day or circadian neuroimaging studies are based on the blood oxygenation level-dependent (BOLD) fMRI. Compared with PET, BOLD fMRI is noninvasive, more cost effective, and easier to apply, thus making it the most widely used imaging method for localizing regional brain function. BOLD studies typically compare fMRI signals during a specific cognitive task with those during a control or baseline condition to obtain task-related brain activation. A large number of BOLD studies have investigated the effects of acute total or partial sleep deprivation on brain activation during performance on a broad range of neurocognitive tasks, including arithmetic calculation,[195] attention,[196–208] decision making,[209–211] emotional processing,[212] episodic memory,[213–215] inhibition control,[216] logical reasoning,[217] spatial navigation,[218] verbal learning,[219,220] visuomotor adaptation memory,[221] and working memory tasks.[222–230] Many BOLD fMRI studies have found changes in neural activity after sleep deprivation. For example, a reproducibility study showed that brain activation patterns were highly correlated across test–retest sessions and the magnitude of decreased activation in parietal regions was preserved and reproducibly correlated with behavioral decline after acute total sleep deprivation.[228] Reduced frontoparietal activation was found during lapses on a visual, selective attention task in addition to decreased overall activation after total sleep deprivation.[199] However, robust interindividual differences in brain responses to sleep loss have also been reported. Individuals cognitively vulnerable to sleep deprivation showed reduced frontoparietal activation, while resilient individuals showed increased parietal activation associated with lapses of attention during total sleep deprivation[201] suggesting a potential neurobiological compensatory mechanism in some individuals.

Far fewer neuroimaging studies have been conducted to examine either time-of-day or circadian phase effects on brain activation. One study used functional near-infrared spectroscopy to examine circadian variability of the hemodynamic response in visual cortex throughout the day from 0800–1800 h, reporting no significant time-of-day influences on visual activation.[231] However, BOLD fMRI studies have shown significant time-of--day effects on brain activation when subjects performed various neurocognitive tasks. For example, Gorfine and Zisapel[232] found that left hippocampal activation was reduced during an autobiographic memory task

at 2200 h compared with 1600 h, indicative of diurnal variation. Vimal and colleagues[233] showed significantly increased BOLD activation in response to light stimuli in the suprachiasmatic nucleus at night compared with midday, while Peres and colleagues[234] demonstrated systematic BOLD signal differences across the day in the motor areas during a self-paced finger-tapping task. Significant time-of-day effects were also observed in the brain orienting attentional system including the inferior parietal and frontal eye field regions during a Stroop-like task, suggesting that bottom-up attention orientation may be vulnerable to circadian factors.[235]

Importantly, a few recent BOLD fMRI studies have demonstrated significant interindividual differences in circadian variation of brain activation and the complex interactions between sleep homeostasis, circadian phase, and genotype. For example, using an auditory 3-back working memory task, Vandewalle and colleagues[236] showed no changes in brain responses during the normal sleep–wake cycle for the putatively less-vulnerable $PER3^{4/4}$ genotype, while reduced activation in the posterior prefrontal area was found in the putatively vulnerable $PER3^{5/5}$ genotype when comparing evening and morning activation during a normal sleep–wake cycle. These authors also reported that blue light increased brain responses in the frontoparietal regions only in $PER3^{4/4}$ individuals in the morning after one night of normal sleep, while blue light increased brain responses in the thalamic and frontoparietal regions only in $PER3^{5/5}$ individuals in the morning after one night of total sleep deprivation.[237] In addition, Schmidt and colleagues[238] showed that morning and evening chronotypes differed in brain activation in the suprachiasmatic area at night during PVT performance. They further found that brain activation associated with conflict processing and inhibition function were maintained or increased in evening chronotypes from the subjective morning to the subjective evening but decreased in morning chronotypes under the same conditions.[239]

While the above findings are informative, one major limitation of task-related BOLD fMRI is that it can only measure *relative* signal changes and lacks absolute quantification of brain activity. Therefore, it is difficult to determine whether the observed BOLD activation changes are due to changes at baseline or changes during performance of specific tasks, or both.

It is also difficult for task-related BOLD fMRI to dissociate the effects of sleep loss, time-of-day, or circadian phase on brain function *per se* and on behavioral performance that subsequently confounds brain activation. In contrast to BOLD, arterial spin-labeled (ASL) perfusion fMRI—a relatively new imaging

technique—can noninvasively measure absolute cerebral blood flow (CBF) that is tightly coupled to regional brain function,[240,241] providing a method for imaging variations of brain function at different time of day or circadian phases or after sleep loss. ASL has been increasingly used to assess waking brain function at task-free resting states as well as during different cognitive tasks.[242,243]

We successfully used ASL to quantify CBF changes after prolonged cognitive workload without sleep loss.[244] Currently, only one published study has used ASL and measured resting CBF changes after one night of sleep restriction.[245] This study reported significantly reduced frontoparietal CBF following sleep loss, but only in participants with significant signs of drowsiness, while nondrowsy participants maintained CBF in the frontoparietal regions and increased CBF in basal forebrain and cingulate regions. These findings also suggest a potential neurobiological mechanism to compensate for drowsiness after sleep loss. Ongoing studies in our group as well as others are using ASL to quantify regional neural activity changes associated with time-of-day variation and sleep deprivation.[246] Our preliminary data from scans during PVT performance in the morning and afternoon in two independent groups also showed significant time-of-day effects. Both morning and afternoon scans showed similar sensorimotor, cingulate, and frontoparietal activation while subjects performed the PVT. However, thalamic activation was observed only in the morning PVT scan, while increased activation in the right frontal eye field was observed in the afternoon PVT scan (Fig. 7.4).

Another emerging imaging method for studying sleep deprivation and time-of-day or circadian phase effects on brain activity is resting-state functional connectivity fMRI (FC-fMRI), which usually uses low frequency fluctuations of resting-state BOLD signal to examine intrinsic and spontaneous neural activity in the absence of external stimuli or tasks.[247,248] Converging evidence from resting-state fMRI studies has indicated an organized mode of resting brain function and identified a number of brain networks associated with different domains of neurocognitive functioning.[249–252] Two recent studies have used FC-fMRI to investigate the effect of one night of either total or partial sleep deprivation on functional connectivity.[253,254] Both studies found that sleep deprivation reduced resting functional connectivity within the default mode network (DMN) and between DMN and its anticorrelated network, suggesting that reduced brain functional connectivity may be a precursor to behavioral impairments from sleep loss. In addition, one recent study used FC-fMRI to

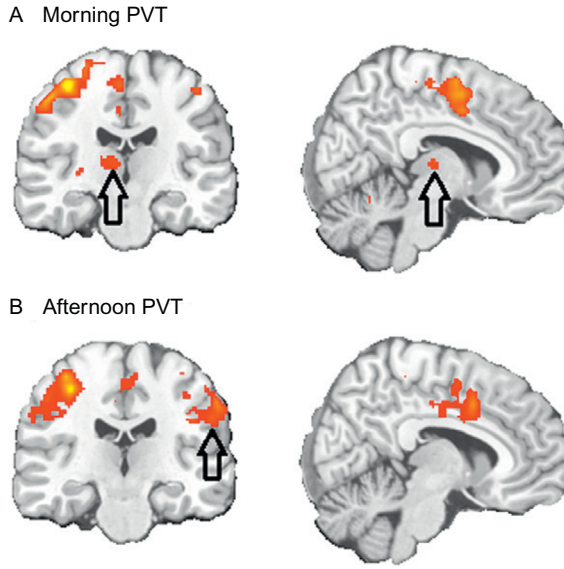

Figure 7.4 Time-of-day effects on absolute cerebral blood flow (CBF) activation during the Psychomotor Vigilance Test (PVT). Twenty healthy adults performed the PVT in the morning (between 0700– and 0900 h) and a separate group of 15 healthy adults performed the PVT in the afternoon (between 1400– and 1700 h)—both groups did so during ASL perfusion f MRI scanning. Brain scans at both times of day showed significant activation in the sensorimotor, cingulate, and frontoparietal regions. However, thalamic activation (indicated by the arrows in A) was only observed in the morning scan while increased activation in the right frontal eye field (indicated by the arrow in B) was observed in the afternoon scan (Hengyi Rao, unpublished data).

examine daily variations in resting brain functional connectivity and found that the DMN and sensorimotor network showed highly rhythmic connectivity patterns while the executive control network was most stable across the day.[255]

Almost all published neuroimaging studies to date have focused on acute total sleep deprivation or time-of-day effects—very few studies have examined the dynamic effects of chronic partial sleep loss and recovery on brain function and their interactions with circadian timing. Findings from the few available ASL and resting-state FC-fMRI studies already provide some important new insights. However, application of these new methods to sleep deprivation and circadian research is still in the early stages and studies are needed to further elucidate the dynamic effects of both acute and chronic sleep loss as well as circadian timing on neural activity.

7. CONCLUSIONS

The circadian drive for wakefulness, the homeostatic drive for sleep, and masking factors simultaneously interact to affect neurobehavioral functioning. Moreover, interindividual differences in circadian parameters, especially phase, and differential vulnerability to sleep loss also markedly affect neurobehavioral responses, suggesting genetic underpinnings. The sleep homeostat and neurobehavioral performance are affected by acute total sleep deprivation and chronic sleep restriction, although the two forms of sleep loss likely differentially affect neural and behavioral responses. Identification of biomarkers that accurately predict alertness and performance via the complex interactions of the sleep homeostatic and circadian systems is of high priority and will aid in predicting performance deficits and implementing countermeasures in a variety of situations in which these two processes are dynamically covarying, such as shift work, jet lag, and imposed acute, chronic, or intermittent sleep loss.

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