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The Circadian Brain and Cognition

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Abstract

Circadian rhythms are inherent to living organisms from single cells to humans and operate on a genetically determined cycle of approximately 24 hours. These endogenous rhythms are aligned with the external light/dark cycle of the Earth's rotation and offer the advantage of anticipating environmental changes. Circadian rhythms act directly on human cognition and indirectly through their fundamental influence on sleep/wake cycles. The strength of the circadian regulation of performance depends on the accumulated sleep debt and the cognitive domain, and it has been suggested to involve the activation of ascending arousal systems and their interaction with attention and other cognitive processes. In addition, attention-related cortical responses show extensive circadian rhythms, the phases of which vary across brain regions. This review discusses the impact of the circadian system on sleep/wake regulation and cognitive performance. It further addresses the health implications of circadian disruption, particularly in relation to mental and neurological disorders.

Contents

INTRODUCTION

Chronobiology studies the timing of physiological and behavioral processes in living organisms. These can be observed at different timescales, ranging from annual (i.e., seasonal rhythms) to monthly (i.e., lunar rhythms), daily (circadian cycles), sleep/wake homeostatic, and ultradian (i.e., <24 hours) rhythms (**Figure 1**). Among them, circadian rhythms are the most robust and well-studied oscillators.

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In humans, circadian clock-induced adaptive arousal mechanisms regulate sleep and wakefulness over the 24-hour cycle. They are precisely timed to interact with hourglass-like sleep homeostatic processes (see the section titled Chronobiology: Basic Definitions in **Supplemental Text**) to achieve a consolidated period of wakefulness during the day and of sleep at night (Dijk & Czeisler 1994). Consequently, sleep loss or shift work disrupts the interplay between these rhythms and may have short- and long-term effects on neurobehavioral functions, mental health, and brain function. Despite the growing body of research on circadian rhythms, particularly following the Nobel Prize–winning discovery of their molecular mechanisms (Burki 2017), relatively few studies have examined the direct effects of endogenous circadian rhythms on human neurobehavioral function. In everyday life, external factors can mask circadian outputs, making it difficult to accurately measure internal rhythms in human behavior (see the section titled Chronobiology: Basic Definitions in **Supplemental Text**). Unmasking these rhythms is therefore essential to understanding their impact on cognition. By illustrating key studies that have unraveled the hands of the endogenous clock in humans, this review aims to provide evidence for a powerful

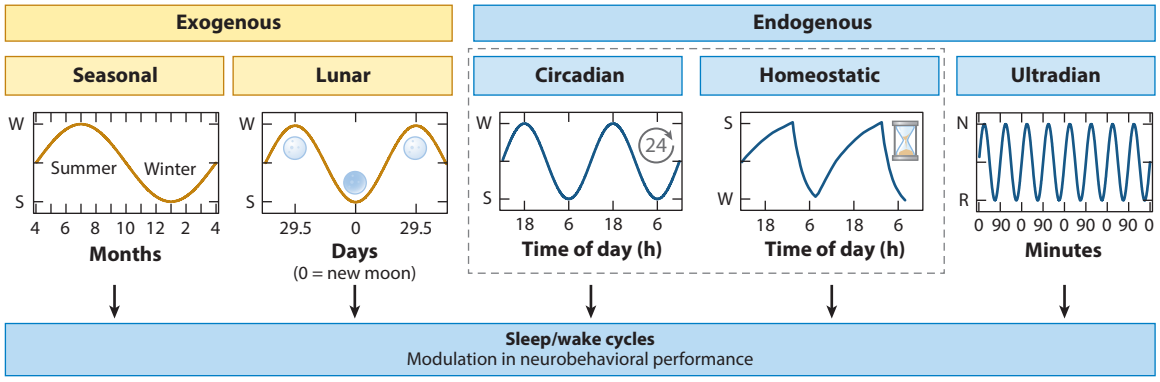

Figure 1

Rhythms at different timescales influence human sleep/wake behavior and neurobehavioral performance. These rhythms can be endogenous, such as the clock-controlled circadian rhythm and the hourglass-controlled homeostatic sleep/wake oscillator, the latter depending on sleep and wake states. Ultradian rhythms are shorter than 24 hours; the most prominent in humans is the 90-minute shift between non-rapid eye movement sleep (N) and rapid eye movement sleep (R) at night. Seasonal and lunar rhythms are both exogenous and endogenous, but there is no evidence so far for endogenous circa-lunar and circa-seasonal rhythms in humans. Environmental seasonal rhythms (photoperiodic changes) and lunar influences on human sleep/wake behavior and cognition have been reported, the latter with inconsistent results. The impact of circadian and homeostatic oscillations on the human sleep/wake cycle and the associated daily modulations in neurobehavioral performance have been widely studied.

modulation of human behavior by circadian rhythms, ranging from the generation of 24-hour sleep/wake cycles to the modulation of cognition and its cerebral correlates. Circadian mechanisms influencing (patho-) physiological processes and the development and progression of a number of neurodegenerative and mental diseases are also briefly discussed. Finally, we propose recommendations and steps to draw attention to the importance of chronobiological aspects in psychological research.

As highlighted in the sidebar titled Neurobehavioral Domains Assessed in Chronobiology, the terminology of cognitive domains remains quite inconsistent across studies in the field of human chronobiology. Therefore, we have chosen to use the term "neurobehavioral performance" when discussing multi-determined tasks from a cognitive perspective. Besides, sustained attention and working memory performance were most consistently assessed in chronobiological paradigms. Our review thus mainly focuses on circadian rhythmicity observed in performance probing these cognitive constructs.

THE CIRCADIAN TIMING SYSTEM IN A NUTSHELL

Over the course of our 24-hour day on Earth, circadian rhythms control the timing of many physiological processes. Unlike diurnal rhythms, which are passively linked to environmental cues (i.e., light/dark or temperature changes), circadian rhythms persist under constant conditions and can be actively entrained to external cues (i.e., Zeitgebers, or synchronizers), such as the environmental light/dark cycle (Roenneberg et al. 2003). Colin Pittendrigh, father of the biological clock, described the key features of the circadian system as "biological activities that characteristically occur once per day in nature [that] continue in laboratory conditions of constant darkness and temperature as a persistent rhythm with a period (τ) that is close to but not exactly 24 h" (Pittendrigh 1993, p. 21); this period is said to be circadian (from the Latin *circa dies*; see also the section titled Chronobiology: Basic Definitions in **Supplemental Text**). Such circadian rhythmicity has been observed at all levels of organization, from the behavior of mammals, flies,

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NEUROBEHAVIORAL DOMAINS ASSESSED IN CHRONOBIOLOGY

Alertness: subjective experience of feeling alert, which parallels arousal levels. The latter is generally defined as the state of being physiologically alert. These have generally been observed to parallel the circadian rhythmicity of core body temperature.

Sleepiness: subjective feeling of sleep need. Although alertness and sleepiness are not necessarily assumed to be reciprocal states, several studies defined alertness as the inverse of participants' scores on sleepiness scales.

Effort (task demands): perceived effort to perform a task/subjective mental effort.

Neurobehavioral performance: multi-determined performance across cognitive domains, ranging from sustained attention to episodic memory, working memory, and/or executive functions. Among those, sustained attention and executive functions with varying levels of working memory load have been most consistently prompted.

Sustained attention or vigilance: the ability to attend over long and generally continuous periods of time for the purpose to detect and respond to relevant stimuli. Generally assessed using 5- or 10-minute simple reaction time tasks.

Executive functions/working memory: the ability to maintain and manipulate information in working memory, mostly measured by using the n-back paradigms (1-, 2-, 3-back) in forced desynchrony and constant routine protocols.

and single cells to the specific activity of enzymes, the activity of ribosomes, and the transcription of identified genes. As Pittendrigh (1993, p. 22) notes, "One of the truly remarkable features of these rhythms is their essentially indefinite persistence (>2 years in some rodents): they are driven by some self-sustaining cellular oscillation as pacemaker of the system."

The Molecular Clockwork

Circadian rhythms are governed by a molecular clock, present in almost all cell types and involving a complex, finely tuned interplay of molecules that create an endogenous circadian rhythm. In mammals, they are regulated by transcriptional mechanisms, cyclic protein turnover, and small molecule inputs (Albrecht 2012). In a simplified scenario, clock genes such as *Clock* and *Bmal* produce proteins that initiate the clock's molecular activities. The CLOCK and BMAL1 proteins (see **Figure 2**) bind to specific regions of DNA and switch on the production of other genes, including *Per* and *Cry* (Albrecht 2023). When these genes are transcribed and translated, they produce PER and CRY proteins (**Figure 2**). As PER and CRY levels increase in the cytoplasm of the cell, they begin to inhibit the activity of CLOCK and BMAL1. As a result, the production of the *Per* and *Cry* genes is slowed, creating a feedback loop that allows the clock to regulate its own activities. In this feedback system, the stability and cellular localization of the clock proteins are tuned by several post-translational modifiers. The whole process takes about 24 hours and repeats itself, helping to regulate various bodily functions. The same transcriptional mechanisms that apply to the clock genes described above are also found outside the clock. These so-called clock-controlled genes (CCGs) (see **Figure 2**) can be regulated by clock proteins. As a result, CCGs are expressed in a timed manner, causing biochemical and physiological pathways to fluctuate. The molecular identification of circadian clock genes up to the level of mammals has revealed a conserved intracellular mechanism that, if disrupted by mutation, can have a significant impact on the behavior of mammals, including humans. Accordingly, natural genetic variants in humans have been identified and studied for their effects on sleep, neurobehavioral performance, and mental health (reviewed in Kyriacou & Hastings 2010).

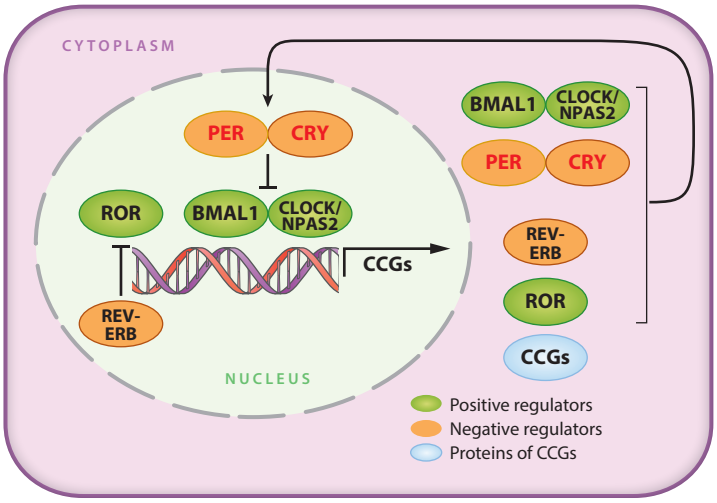


Figure 2

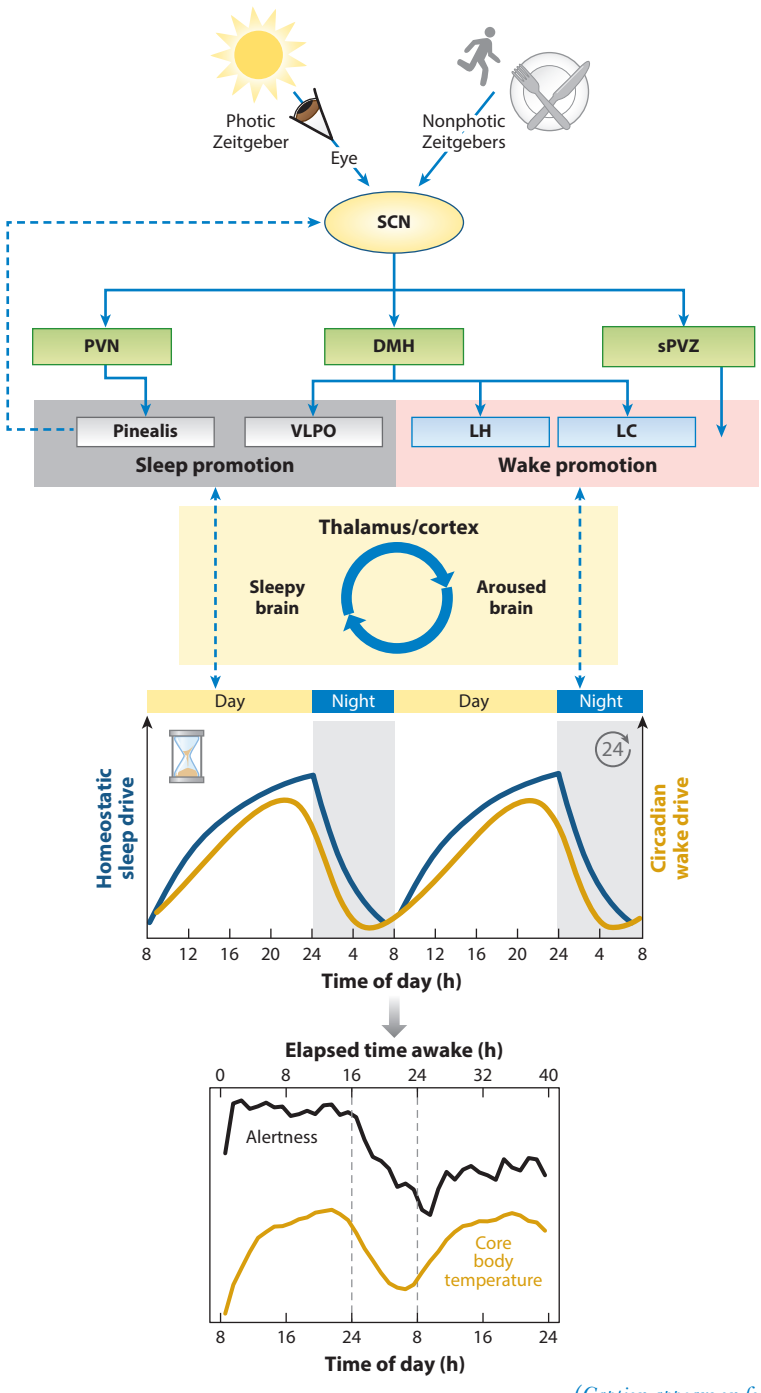
Modeling the molecular mechanism of the circadian clock. The light purple area represents the cytoplasm and the light green circle represents the nucleus. The green ovals represent positive regulators of the clock, while the orange ovals represent negative regulators of the clock mechanism. The blue oval represents the proteins of clock-controlled genes (CCGs). In mammals, the core clock genes are *Bmal1* and *Clock* (and its homolog *Npas2* in the nucleus), which activate the expression of target genes such as *Per* and *Cry*. PER and CRY proteins (*red*) dimerize, enter the nucleus, and repress BMAL1/CLOCK(NPAS2) activity, that is, their own transcription. The nuclear receptors of the REV-ERB and ROR families regulate the expression of the *Bmal1*, *Clock*, and *Npas2* genes by binding to RORE elements, thereby repressing (REV-ERB) or activating (ROR) transcription. Figure adapted from Albrecht (2023).

The Central Circadian Clock

The circadian timing system consists of a myriad of cellular clocks throughout the body, but the principal mammalian circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Hastings et al. 2019). The human SCN is located bilaterally in the anterior hypothalamus above the optic chiasm, and it has approximately 50,000 neurons at each site that play a critical role in regulating circadian behavior (Moore 2013). Damage to hypothalamic regions in or near the SCN in humans results in post-traumatic irregular sleep/wake and body temperature rhythms as well as impaired waking function (Cohen & Albers 1991, DelRosso et al. 2014). A unique feature of the SCN is that neurons form an interconnected network of cells capable of self-sustaining, circadian oscillations of both neuronal activity and gene expression, even in the absence of external stimulation (Hastings et al. 2019). Neuropeptides play a key role in synchronizing circadian rhythms within the SCN, where interactions between neurons and glial cells are critical for rhythm regulation (Ono et al. 2024). The SCN is thus an integrating brain structure that synchronizes molecular timing, glial cell activity, and neuronal firing rhythms on a circadian timescale.

Afferents to the Central Clock

The SCN has three major afferent connections. The most important is the retinohypothalamic projection, which transmits photic information via specific retinal photoreceptors in the eye to the central clock in the SCN (Schmidt et al. 2011) (**Figure 3**). The other two robust afferent projections are the median raphe serotonergic pathway and the geniculohypothalamic (GHT)



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

A major input to the central clock, the suprachiasmatic nucleus (SCN), comes from intrinsically photosensitive retinal ganglion cells via the retinohypothalamic tract. This pathway is critical for photic entrainment of the circadian clock. The SCN also receives nonphotic input via the median raphe serotonergic pathway and the geniculohypothalamic tract (GHT), which is modulated by activity and sleep. Meal timing can also act as indirect nonphotic input to the SCN via its effect on peripheral circadian clocks. The SCN projects directly to important regions in the hypothalamus involved in sleep/wake regulation. These are the paraventricular nucleus (PVN), the dorsomedial hypothalamus (DMH), and the subparaventricular zone of the hypothalamus (sPVZ). The DMH projects to sleep- and wake-promoting areas, including the ventrolateral preoptic nucleus (VLPO) for sleep promotion and the lateral hypothalamus (LH) and locus coeruleus (LC) for wake promotion. These main sleep/wake promoting subcortical nuclei interact and modulate thalamic and cortical arousal. In diurnal animals, including humans, and under entrained conditions, the SCN promotes wakefulness during the subjective day with a maximal drive in the evening and minimum drive during the night, when melatonin is actively secreted in the pineal gland (pinealis) under the control of the SCN and via the PVN. The hourglass-like homeostatic sleep process increases with increasing amount of time spent awake and dissipates during sleep. Both processes interact to modulate alertness, which is anchored to the core body temperature rhythm. Figure adapted from Meyer et al. (2022) (upper portion) and Dijk et al. (1992) (lower portion).

input from the thalamic intergeniculate leaflet (IGL) (Morin 2013). IGL neurons are sensitive to changes in general illumination intensity (Harrington & Rusak 1989) and convey photic information to the SCN (Zhang & Rusak 1989), while the raphe-SCN pathway represents a nonphotic input to the SCN modulated by activity and sleep (Mistlberger & Skene 2005). Photic and nonphotic information shape the clock in an adaptive manner to modify the phase and period of circadian rhythms. These so-called Zeitgebers are used to keep the central circadian clock in sync with solar time, so that it can accurately predict and anticipate dawn and dusk. More recently, inputs to the SCN from the ventral tegmental area and basal forebrain have also been suggested (Ono et al. 2024). As the SCN contains receptors for melatonin, estrogen, androgen, and progesterone, humoral inputs can also modulate the electrical activity of SCN neurons and adjust the phase of the SCN clockwork (Belle 2015).

Efferents from the Central Clock

The SCN communicates its rhythmic output to the brain and the rest of the organism via humoral and neural pathways (Kalsbeek et al. 2011). Direct projections from the SCN are rather limited and are generally confined to a few hypothalamic nuclei, the main targets being the paraventricular nuclei (PVN), the preoptic area, and the dorsomedial hypothalamus (DMH) (Buijs & Kalsbeek 2001; see also **Figure 3**). More recently, monosynaptic projections from a small number of neurons in the SCN to the central amygdala have also been identified (Francois et al. 2023). While the function of most SCN projections to downstream brain regions is still not fully understood, the circuitry underlying circadian arousal generation has been partially mapped (Starnes & Jones 2023). In this circuit, the SCN projects both directly and indirectly to the DMH, which acts as a relay for SCN signals and integrates circadian and sleep/wake information (Chou et al. 2003). DMH projections inhibit the activity of sleep-promoting neurons in the ventrolateral preoptic area (VLPO), while other DMH projections activate wake-promoting orexin (hypocretin) neurons in the lateral hypothalamus (LH) (**Figure 3**), which also show circadian rhythmicity (Zeitzer et al. 2003). This leads to stimulation of the ascending reticular activating system, which projects to the thalamus and cortex to promote and maintain wakefulness and associated arousal levels (Scammell et al. 2017). Thus, it is likely that the DMH integrates circadian signals to actively promote wakefulness at certain times and sleep at other times (Mistlberger 2005). Direct SCN projections to the VLPO and the medial preoptic area may also play a role, but their functional

importance remains untested (Deurveilher & Semba 2005). In addition, the noradrenergic locus coeruleus (LC) system, an important brain region strongly involved in arousal and sleep/wake functions, receives circadian input via the SCN–DMH pathway, the latter as a critical relay. Lesions of the DMH abolished circadian changes in LC activity, confirming a dominant role for the SCN–DMH–LC axis in the circadian arousal regulation (Aston-Jones et al. 2001). Neural connections between SCN and sleep/wake-related structures are reciprocal (Deboer et al. 2003), which may ensure the stable yet adaptive rhythmicity of the daily sleep/wake cycle and associated changes in arousal and alertness (Deurveilher & Semba 2005).

Brain Regional and Peripheral Circadian Clocks

Notably, molecular clocks have been shown to tick across a wide range of brain areas, and their circadian phases and anatomical relationships to central pacemakers suggest new ways of understanding the mechanisms of interaction between circadian clocks, sleep, and neurobehavioral performance (Kyriacou & Hastings 2010). The clock may thus act globally on waking performance through arousal-promoting mechanisms but also regionally according to task-specific demands and their underlying cerebral networks.

The impact of peripheral clocks on sleep/wake regulation and associated waking function is an emerging area of research in neuroscience. Local clocks may modulate the release of hormones and neurotransmitters that affect brain function both directly and indirectly by regulating systemic physiology, which in turn affects brain states. Disruption of these clocks due to factors such as irregular sleep patterns, jet lag, or shift work can also lead to cognitive impairment and mood disorders (Arble et al. 2015). It is also possible that disturbances in peripheral clocks lead to disrupted sleep patterns and, conversely, altered sleep/wake cycles desynchronize clocks, affecting overall health and cognitive function.

In summary, the circadian timing system forms a multi-layered network, from genes to behavior, to enable optimal alignment with environmental rhythms and synchronization of neurophysiological, metabolic, and biochemical processes within an organism. Its role in structuring human sleep/wake behavior and cognitive functions is highlighted in the next sections.

CIRCADIAN RHYTHMS AND SLEEP/WAKE STATES

The alternating pattern of sleep and wakefulness in humans has been attributed to the interplay between circadian and sleep homeostatic drives (Borbély 1982, Daan et al. 1984, Edgar et al. 1993). In the past four decades, the two-process model of sleep/wake regulation (**Figure 3**) has served as the main conceptual framework in sleep research. Sleep homeostasis is expressed by a monotonic increase in sleep pressure during sustained wakefulness and its dissipation during sleep (Borbély & Acherman 2005). The latter reflects an hourglass-like process that increases progressively with the amount of time spent awake and decreases exponentially during sleep. Night-time dynamics of electroencephalography (EEG)-derived sleep slow-wave activity (SWA) have been considered as valid markers of sleep homeostasis, with higher SWA indicating a higher need for sleep (Achermann et al. 1993). Under entrained conditions (see the section titled Chronobiology: Basic Definitions in **Supplemental Text**), the SCN circadian master clock provides temporal organization to the sleep/wake cycle through adaptive arousal mechanisms (i.e., increasing wake promotion over the day and decreasing sleep promotion over the night) that oppose the homeostatic drive for sleep (Dijk & Czeisler 1994). Thus, maximal circadian wake promotion, or the wake maintenance zone, occurs toward the end of the waking day in order to counteract the increasing sleep pressure (Dijk & Czeisler 1994, Lavie 1986, Strogatz et al. 1987). Conversely, the peak of circadian sleep promotion occurs toward the end of the biological night,

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facilitating sleep consolidation despite the progressive dissipation of homeostatic sleep pressure (**Figure 3**).

Besides its role in sleep timing, the circadian system also contributes to structural changes in sleep (Dijk & Czeisler 1995), including the composition of ultradian alternation between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep throughout the night. REM sleep shows a clear circadian modulation peaking in the late night to early morning hours, indicative of a circadian sleep-facilitating window (Carskadon & Dement 1975, Czeisler et al. 1980, Dijk et al. 1997, Lavie 2001). While the NREM sleep–characteristic SWA has also been shown to exhibit circadian rhythmicity, it appears to be comparatively more influenced by sleep homeostatic factors (Dijk & Czeisler 1995, Lazar et al. 2015). As a result, the interaction between these processes, and in particular their phase relationship, significantly affects sleep characteristics. Thus, sleep during the biological day not only will result in shorter sleep durations but also will exhibit different structural and electrophysiological features, including variations in REM/NREM sleep amounts, SWA, or other electrophysiological properties such as sleep spindle characteristics (Dijk & von Schantz 2005). This is important because such properties have been linked to a number of plasticity and learning processes that may be more or less efficiently expressed depending on when we choose to schedule sleep over the 24-hour cycle (Kyriacou & Hastings 2010).

The use of phenomenological models of sleep/wake dynamics, such as the two-process model, has been successful in predicting a number of sleep/wake behaviors and interindividual differences in their expression. Quantitative differences in these processes (e.g., circadian phase, amplitude, period, homeostatic slope; see the section titled Chronobiology: Basic Definitions in **Supplemental Text**) and their phase relationships have for example been shown to underlie the preferred timing for sleep or chronotype (Duffy et al. 1999, 2001; Mongrain et al. 2006) as well as differences in sleep duration (Aeschbach et al. 1996) and sleep structure (Viola et al. 2007). Notably, such phenomenological models have subsequently been complemented by the emergence of physiologically based mathematical models (e.g., Postnova 2019) that consider how circadian and homeostatic processes impinge upon key arousal-promoting nuclei in the brainstem and hypothalamus (**Figure 3**). They basically model the interactions among these neuronal populations and thereby offer physiological insights that can be readily applied to predict and provide a deeper understanding of in-vivo observed fluctuations in sleep propensity, interindividual differences in sleep timing and duration, and neurobehavioral performance modulation under various conditions (e.g., sleep loss, sleep/wake cycle fragmentation, shift work).

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Finally, it should be noted that the traditional view that sleep primarily serves homeostasis through a single output of SWA, and that circadian rhythms merely dictate the timing of sleep, is currently being challenged (Franken & Dijk 2024). Sleep is increasingly understood not only as a global brain state but also as a phenomenon that can be expressed locally at the level of brain regions in a use-dependent manner. As a consequence, activity during wakefulness influences local cortical sleep depth (Huber et al. 2004, Krueger et al. 2019). Furthermore, characterizing the circadian process as solely driven by the SCN is too simplistic. As highlighted in the previous section, molecular circadian clocks exist not only in the SCN but also throughout the brain and body tissues, highlighting a global and local interplay between sleep regulation and circadian rhythms.

CIRCADIAN RHYTHMS AND COGNITION

The circadian clock exerts a profound influence that extends beyond mere sleep regulation. This is evidenced by Ebbinghaus's [1913 (1885)] early observations that the learning of nonsense syllables changes over the course of the day. Kleitman was the first to systemically assess the impact of

circadian rhythmicity on human wake functions. He observed that performance on simple repetitive tasks parallels the daily modulation in core body temperature (Kleitman et al. 1938; see Schmidt et al. 2007 for a review). He postulated that accuracy and speed in these tasks depend on the degree of muscle tone and, in turn, on the metabolic activity of the cells of the cerebral cortex. The circadian-related increase in body temperature would thereby indirectly speed up cognitive processing. Subsequent research has at least partly corroborated his theory that core body temperature per se can modulate human neurobehavioral performance (Wright et al. 2002).

The fundamental influence of the circadian clock on waking performance has been revealed using forced desynchrony (FD) and constant routine (CR) protocols. These protocols isolate participants from environmental cues and subject them to non-24-hour sleep/wake schedules in the laboratory for days to weeks. The FD procedure forces a progressive desynchronization of the imposed sleep/wake cycle from the endogenous circadian cycle. The latter begins to run free (see the section titled Chronobiology: Basic Definitions in **Supplemental Text**) by adopting its endogenous circadian period (Wang et al. 2023). In addition to enabling the assessment of the circadian period, this paradigm offers a unique advantage in that it permits the mathematical separation of the influence of homeostatic sleep pressure from that of the circadian pacemaker. This allows the status of the sleep homeostasis to be studied at virtually any circadian phase. In parallel, CR protocols have been developed to detect endogenous circadian rhythms classically embedded in the sleep/wake cycle. During such a protocol, subjects must remain awake under constant environmental conditions for a period significantly longer than 24 hours. By tightly controlling and minimizing rhythmic external masking factors, such as posture changes, light levels, food intake, and physical activity, the protocol enables the precise quantification of the endogenous phase or amplitude of circadian rhythmicity and its influence on physiology and behavior, including alertness and neurobehavioral performance.

These studies have been pivotal in separating the effects of sleep/wake history (sleep homeostasis) from those of the circadian clock per se and in assessing their respective effects on neurobehavioral performance. Most of these early studies, however, used tasks that are currently classified as multi-determined from a cognitive perspective and are referred to here as waking or neurobehavioral functions. In a second step, we discuss FD and CR studies that have conducted a finer-grained analysis of the cognitive domains examined. This illustrates that the latter may influence the strength with which the clock influences human waking function. This section focuses on the domains that have been most consistently assessed in the context of chronobiological FD and CR paradigms (see the sidebar titled Neurobehavioral Domains Assessed in Chronobiology).

Circadian Rhythms, Sleep Homeostasis, Alertness, and Neurobehavioral Performance

FD and CR protocols provide strong evidence for a concomitant circadian and sleep homeostatic modulation of alertness and neurobehavioral performance levels. Results from these studies revealed that when both processes are entrained (see the section titled Chronobiology: Basic Definitions in **Supplemental Text**), stable performance levels can be achieved over a classical 16-h waking day. This is due to the increasing circadian arousal signal counteracting the detrimental effects of increasing duration of wakefulness on waking function (Cajochen et al. 1999, Dijk et al. 1992, Wright et al. 2002, Wyatt et al. 1999), as exemplified for attention performance in **Figure 4**. Notably, stable performance levels over 16 hours of continuous wakefulness can only be achieved when the waking period is initiated at a specific circadian phase (i.e., during the rising phase of the core body temperature rhythm). When wakefulness is scheduled outside this optimal circadian

window, such as in shift work, even shorter periods of prior wakefulness can lead to performance deficits. This highlights the importance of the phase relationship between the circadian pacemaker and the sleep/wake cycle in achieving stable neurobehavioral states (Dijk & Czeisler 1995, Hull et al. 2003, Wright et al. 2002, Zhou et al. 2011). In individuals subjected to conditions of sleep deprivation (e.g., CR protocols), marked performance decrements are observed when wakefulness is extended into the biological night due to reduced circadian arousal promotion and unopposed homeostatic sleep pressure levels (e.g., Cajochen et al. 1999). This effect is likely to contribute to the increased frequency and severity of human errors at night, particularly in the early morning

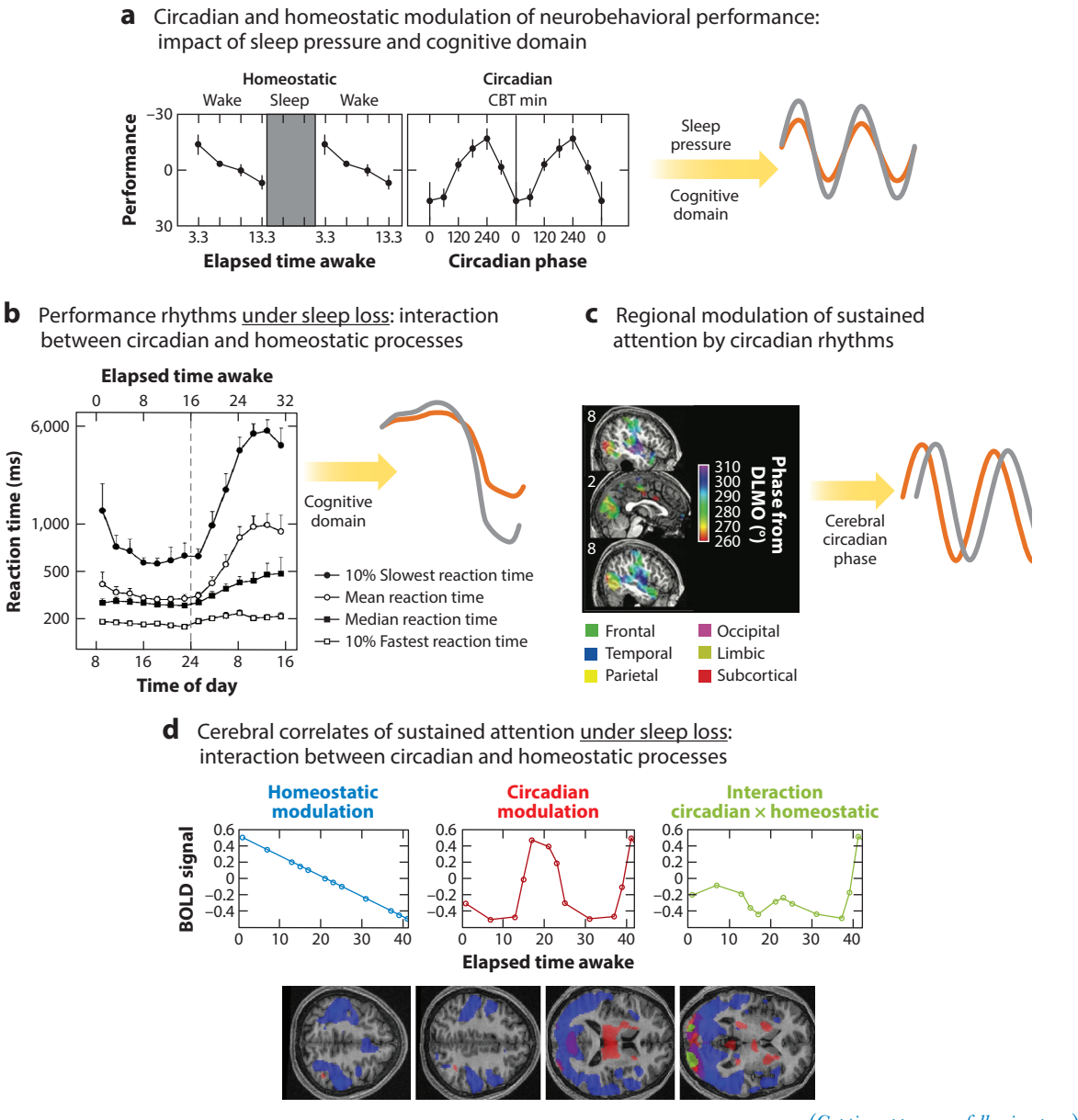

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Figure 4 (*Figure appears on preceding page*)

Overview of the impact of circadian rhythms and sleep homeostasis on neurobehavioral performance. (*a*) Illustration of circadian and homeostatic modulation of neurobehavioral performance as derived from forced desynchrony studies [median response times on the Psychomotor Vigilance Task (PVT)] (left portion of the panel adapted from Wyatt et al. 1999). Time courses are illustrated as double plots of main effects of prior scheduled wakefulness (sleep homeostatic influence) and of circadian phase [0 = core body temperature (CBT) minimum]. Homeostatic sleep pressure and cognitive domain have been shown to affect the amplitude of circadian performance rhythms (*gray* and *orange lines*). (*b*) Illustration of performance modulation over a 40-hour sleep deprivation protocol under constant routine (CR) conditions (different reaction time ranges on the PVT) (left portion of the panel adapted from Cajochen et al. 1999). Time courses are expressed with respect to elapsed time since scheduled wakefulness and the corresponding time of day are also indicated. The vertical reference line indicates the transition of subjects' habitual wake time to bedtime. The cognitive domain has been shown to influence the strength of this modulatory pattern (*gray* and *orange lines*). (*c*) Circadian phase map of brain responses to PVT performance during a CR protocol (left portion of the panel adapted from Muto et al. 2016). The local response phase is displayed according to the color scale [°; dim light melatonin onset (DLMO) = 0°] and superimposed on individual normalized T1 magnetic resonance (MR) scan. Coordinates are in millimeters along the *z*, *y*, and *x* axes. Cortical responses show significant circadian rhythmicity, with the phase varying across brain regions (cerebral circadian phases). (*d*, *top*) Illustration of dimensionless fixed-effects fMRI contrasts testing (from left to right) a decrease in response with increasing sleep pressure during wakefulness (linear/homeostatic modulation; *blue graph*), their fluctuation in association with mean melatonin level (circadian modulation; *red graph*), and the interaction between these two factors (*green graph*). (*d*, *bottom*) Illustration of significant effects of homeostatic sleep pressure (*blue*), circadian rhythmicity (*red*), and their interaction (*green*), displayed at $P < 0.05$ (family-wise-error) corrected over an individual normalized T1-weighted MR scan. Panel adapted from Muto et al. (2016). Abbreviation: BOLD, blood-oxygen-level-dependent.

hours when circadian sleep promotion is at its highest (Cohen et al. 2010, Grady et al. 2010). In the same vein, neurobehavioral performance under conditions of sleep loss (increased homeostatic sleep pressure levels) is partially rescued when wakefulness is extended from the night into the next day, thanks to the activation of circadian arousal-promoting signals (Cajochen et al. 1999). Such beneficial effects of circadian arousal promotion under conditions of sleep loss appear to be particularly strong during the wake-maintenance zone (Shekleton et al. 2013). Furthermore, neurobehavioral performance deficits have also been shown to accumulate with increasing days of circadian misalignment, thereby underscoring the circadian mechanism by which shift work can affect neurobehavioral performance (Cohen et al. 2010, Silva et al. 2010, Wright et al. 2006).

Circadian Performance Rhythms: Impact of Cognitive Domain?

There is a debate as to whether circadian rhythms uniformly regulate cognitive performance via general arousal mechanisms (possibly tied to body or brain temperature changes) or whether tasks targeting different cognitive domains vary in circadian phase and amplitude. From a neuroanatomical perspective, the first hypothesis would generally imply equal circadian variations across cerebral functions (i.e., global metabolic changes in the challenged brain areas mediated by circadian arousal), whereas the second assumption would imply more regionally different (or region-specific) variations in cerebral activity.

Circadian performance modulations that are phase aligned with the circadian rhythm of core body temperature have been observed for performance in a variety of tasks, including addition, code substitution or word pair learning, prose recall and procedural memory, selective attention, language processing, or planning performance (e.g., Blatter et al. 2005; Cajochen et al. 1999, 2004; Horowitz et al. 2003; Johnson et al. 1992; Rosenberg et al. 2009; Wright et al. 2002; Wyatt et al. 1999). Such unequivocal modulation across a variety of cognitive domains suggests that the circadian arousal signal acts downstream of attentional and other cognitive processes to induce a circadian modulation of performance that is phase anchored to the rhythms of alertness.

Interestingly, a pacemaker-accumulator model has also been suggested to explain results on circadian and wake-dependent fluctuations in short-term interval timing ranging from seconds to hours in humans (e.g., Späti et al. 2009, 2015). However, while temporal self-location has been

known to be based on a biological clock located within the hypothalamus, the mechanisms that participate in temporal position to the cognitive level and the way the latter integrates with the biological clock remain poorly understood. One study (Späti et al. 2009) observed an overestimation of clock time during prolonged wakefulness as well as a significant diurnal oscillation in estimation errors roughly paralleling the circadian rhythmicity in core body temperature. In a follow-up study (Späti et al. 2015), putative circadian and sleep-homeostatic effects were assessed on interval timing, and pacemaker-based mechanisms were assessed by measuring timing performance under entrained and free-running conditions. The authors could confirm the action of opposing oscillatory time courses for time estimation and production tasks that are consistent with the hypothesis that a pacemaker emitting pulses at a rate controlled by the circadian oscillator and increasing with time awake determines human short-term interval timing.

Attention and (circadian) arousal modulation are closely linked. An organism with impaired arousal would also have impaired attention (Gitelman 2003). Nevertheless, the converse is not necessarily true, as individuals who are normally aroused may also exhibit attentional deficits. Furthermore, the capacity to maintain attention during the testing period is a fundamental prerequisite for optimal performance in almost all cognitive tests.

FD and CR studies do not provide convincing evidence to support previous studies conducted under natural day/night cycles that suggest different circadian phases for different cognitive processes (e.g., Folkard & Totterdell 1994, Folkard et al. 1976). At the same time, the amplitude of the circadian modulation of performance has been shown to be fairly consistently influenced by the cognitive domain. Changes in circadian amplitude are further influenced by sleep pressure—being lower under reduced sleep pressure and higher otherwise (e.g., Wyatt et al. 1999, Zhou et al. 2011; see **Figure 4**).

The impact of the cognitive domain on the modulation of circadian performance can be illustrated quite convincingly by two studies that examined the effect of circadian phase and varying levels of sleep pressure on a range of cognitive domains using a CR (Lo et al. 2012) and an FD (Santhi et al. 2016) protocol. Both studies used the same task setting, which was selected to recruit different cognitive domains by presenting redundancies and partial functional overlaps to counter the inherent difficulty that no cognitive task is process pure (Lo et al. 2012). The battery contained subjective rating scales and objective performance tests including subjective sleepiness or alertness [Karolinska Sleepiness Scale (KSS)], sustained attention [Psychomotor Vigilance Task (PVT) and Sustained Attention to Response Task (SART)], working memory/executive function measures [visual, verbal, and spatial 1-, 2-, and 3-back (depending on whether a presented item corresponds to the one presented 1, 2, or 3 trials before)], and corresponding subjective effort scales [Visual Analogue Scales (VAS)] as well as tasks probing temporal (fixed/random interval repetition task) and motor (pursuit tracking task) control. The administration of such an extensive test battery allowed the extraction of more than 50 performance measures and the characterization of circadian modulation across domains. A significant effect of circadian phase was observed in approximately 60% of the measures. As expected, overall performance fluctuations in these tasks were phase aligned to the profile predicted by the two-process model of sleep/wake regulation: Performance dipped in the early morning, coinciding with the declining phase of melatonin, and peaked in the evening prior to melatonin secretion. Similarly, the decline in performance due to sleep loss was modulated by the circadian phase, so that it was more pronounced when wakefulness occurred during the night. Notably, however, quantitative differences in circadian effects emerged across cognitive domains. Effect sizes quantifying the strength of circadian modulation were generally largest for subjective measures (sleepiness, mood, effort to perform) and sustained attention measures (slowest reaction times and lapses on a PVT). Circadian effects on executive measures appeared to be comparatively smaller and did not vary consistently with increasing working memory load

(1-back to 3-back). Similarly, the circadian influences on sleepiness and attention were remarkably strong in another study, although circadian effects were also observed on inhibitory control as assessed by the Stroop task (Burke et al. 2015). Overall, these findings are consistent with previous research showing that subjective effort, mood, alertness, and sustained attention are more vulnerable to sleep deprivation than working memory, executive function, or motor control (Killgore 2010, Lim & Dinges 2010, Lo et al. 2012). In addition, dissociation studies and meta-analyses no longer support the hypothesis that sleep loss per se (or staying awake during an unfavorable circadian phase) has a greater impact on executive frontal control processes (Blatter & Cajochen 2007) than on nonexecutive task components (Lim & Dinges 2010, Lo et al. 2012, Tucker et al. 2011).

Finally, in one of these studies (Santhi et al. 2016), principal component analysis was used to highlight the commonalities between tasks rather than the specific cognitive demands of particular tasks. Three dimensions were identified across the aforementioned performance measures: effort, speed, and accuracy. The largest circadian effect sizes were found for effort and accuracy in this task set.

Circadian Performance Rhythms: Interindividual Differences

Individuals respond more or less successfully to task demands, raising the question of trait-like modulation of neurobehavioral performance by the circadian clock and its interaction with sleep homeostasis. Vulnerability has been observed to vary across cognitive domains, with individuals being more vulnerable to sleep loss and adverse circadian phase in one domain and more resilient in others (Frey et al. 2004, Sprecher et al. 2019, Van Dongen et al. 2004). Trait-like responses have for example been observed for sustained attention, short-term memory, processing speed, sleepiness, and mood as well as for inhibitory control and selective visual attention (e.g., Sprecher et al. 2019, Van Dongen et al. 2004). While subjective measures of alertness and sustained attention have been observed to be most influenced by sleep and circadian phase (e.g., Lo et al. 2012, Santhi et al. 2016), performance on executive tasks has been suggested to show stronger trait-like responses to sleep loss and adverse circadian phase (Archer et al. 2018). This has been illustrated, for example, by studies stratifying for a polymorphism in the human clock gene PER3, which confers susceptibility to sleep loss through altered SWA dynamics and thereby potentially through sleep homeostatic processes (Viola et al. 2007). Genotype effects were most pronounced when executive function (N-back performance) was assessed during the night, while circadian and sleep loss–related modulation of subjective alertness and sustained attention did not differ between genotypes (Groeger et al. 2008, Lo et al. 2012). However, the effect size of genotype on executive performance was smaller than the effects of sleep loss and circadian phase per se. Nevertheless, such genotype-specific effects suggest that the top-down executive control mechanisms required for task performance are ultimately affected in a trait-like manner under conditions of sleep loss and circadian misalignment.

Another study further assessed circadian performance rhythms according to biological sex (Santhi et al. 2016) and observed that although circadian effects were seen in both men and women, the amplitude of the circadian modulation was larger in women in a series of measures, so that their performance was more impaired in the early morning hours.

Circadian Performance Rhythms: Cerebral Underpinnings

Circadian rhythms may affect cognitive performance uniformly through general arousal mechanisms and/or in a region-specific manner according to the cognitive domain which is being challenged. Within this perspective, circadian arousal could selectively control cortical resources that underlie task performance at the cerebral level. For example, robust circadian dynamics

of cortical excitability evoked by transcranial magnetic stimulation correlate with circadian performance modulation (Ly et al. 2016). Animal and molecular studies further provide compelling evidence for a profound impact of circadian rhythmicity on brain function (Kyriacou & Hastings 2010), whether through modulation of synaptic plasticity (Frank & Cantera 2014) or through neuromodulatory effects associated with circadian arousal signals (Aston-Jones 2005). However, human studies assessing the functional neuroanatomy of circadian and homeostatic effects on neurobehavioral functions remain scarce, also because of the challenges associated with conducting FD and CR studies in in-vivo neuroimaging settings.

Circadian Performance Rhythms: Implication of Arousal-Promoting Brain Centers

Functional magnetic resonance imaging (fMRI) studies on extreme chronotypes under natural light/dark cycles revealed initial indirect evidence for circadian and homeostatic influences on the neural bases of sustained attention and working memory (Schmidt et al. 2009, 2012, 2015). These studies mainly indicated chronotype-dependent hypothalamic and brainstem LC activations supporting sustained attention performance during the evening hours surrounding the onset of melatonin secretion and thus high circadian arousal promotion. During this time window, attention-related blood-oxygen-level-dependent (BOLD) signals in the LC and anterior hypothalamus were enhanced in evening types who also showed more stable performance levels (Schmidt et al. 2009). Furthermore, task-related BOLD activation in the anterior hypothalamus (presumably including the suprachiasmatic area) appeared to be proportional to the degree of accumulated sleep pressure as assessed by the amount of SWA during the following night. In the same vein, hypothalamic BOLD activity was positively linked to circadian wake-promoting strength in a homeostatic-dose-dependent manner in another study (Reichert et al. 2017). Given that both the hypothalamus and LC are critically involved in circadian arousal promotion (Aston-Jones et al. 2001) and that SCN activity is modulated by homeostatic sleep pressure (Deboer et al. 2003), these findings provided first evidence for an influence of the homeostatic and circadian interactions on the neural activity underlying human attention.

Thalamic activity has been suggested to mediate the interaction between attention, task engagement, and arousal in humans (Portas et al. 1998), and it has been shown rather systematically to be more activated under conditions of acute sleep loss (Ma et al. 2015). Similarly, during adverse circadian phases, thalamic engagement and its functional connectivity with task-relevant brain areas appeared less efficient over time into task in subjects with greater attentional instability during PVT performance (Maire et al. 2015). Enhanced thalamic activation was also observed to maintain stable performance during adverse circadian phases (early morning/night) in a sustained attention task. Specifically, under sleep loss, thalamic activation linked to optimal PVT performance (fastest reaction times) paralleled the time course of subjective alertness with nocturnal peaks and diurnal troughs (Maire et al. 2018).

Local Modulation of Human Brain Responses by Circadian Clocks

The modulation of sustained-attention-related cortical activation patterns by the circadian clock and by sleep debt has been most extensively assessed by Muto and colleagues (2016). In a neuroimaging study, these authors quantified changes in brain responses to a sustained-attention task (PVT) over 13 fMRI sessions during a CR protocol. A general decrease in activity was observed over the protocol in a large set of attention-related cortical areas (mainly high-order association cortices of the frontal, parietal, insular, and cingulate cortices as well as visual and sensorimotor cortices). In line with Maire et al. (2018), subcortical and mainly thalamic activation showed

primarily a circadian modulation closely following the melatonin profile. The high sampling rate of the fMRI sessions further allowed the detection of nonlinear dynamics as predicted by the interaction between circadian and sleep homeostatic processes in a subset of cortical areas (mainly in occipital regions; see **Figure 4*d***). A periodicity analysis further revealed strong circadian rhythmicity in task-related BOLD responses over almost the entire cortical mantle, except for the dorsolateral prefrontal cortex. Notably, the phase of circadian modulation largely varied across brain regions, such that occipital and limbic regions showed an earlier timing of maximal responses compared to associative areas in the temporal and prefrontal cortex. These results indicate a region-specific circadian modulation of attentional brain responses and support the notion that task performance is locally altered over the 24-hour cycle. In the same study, brain responses underlying executive responses (N-back paradigm) showed a clear circadian oscillation in the bilateral anterior insula in synchrony with the circadian melatonin rhythm. This finding speaks against a global, nonspecific circadian influence; instead, it further supports a region-specific and task-dependent circadian signal underlying neurobehavioral performance under sleep deprivation conditions.

Thus, the circadian timing signal from the central clock in the SCN may, to some extent, be locally modified in response to the demands of a task. As a consequence, specific behaviors may be impaired by sleep loss, depending critically on when they occur within the 24-hour cycle. Interestingly, task-specific modulation of BOLD responses has also been observed on the timescale of seasonal modulations (Meyer et al. 2016).

Light and Cognition

Light reflects the main Zeitgeber for the circadian timing system. Light exposure in the evening typically delays circadian rhythms, shifting biological activities later. Conversely, morning light exposure advances these rhythms, shifting activities earlier (Khalsa et al. 2003). The retinohypothalamic tract transmits light from intrinsically photosensitive retinal ganglion cells (ipRGCs) directly to the SCN (**Figure 3**). These ganglion cells not only play an important role in circadian photoentrainment but also directly innervate key brain regions involved in the maintenance of neurobehavioral functions. In humans, light, especially in the short wavelength range, acutely increases alertness and attention, suggesting the involvement of ipRGCs that are optimally sensitive to 460–480 nm (Cajochen 2007, Schöllhorn et al. 2023, Vandewalle et al. 2009). In addition to the wavelength of light, the duration and intensity of light exposure also modulate brain responses in cognitive tasks, initially in alertness-related subcortical structures (hypothalamus, brainstem, thalamus) and limbic areas (amygdala and hippocampus), followed by modulations of activity in cortical areas, which may ultimately affect waking functions in a widespread manner (Vandewalle et al. 2009). Studies in animals have found that ipRGCs also project to brain regions such as the perihabenular nucleus (implicated in mood regulation) and the prefrontal cortex, which is also central to executive function, suggesting that ipRGCs may play a broader, as yet unexplored, role in modulating cognitive performance (Mahoney & Schmidt 2024). While the effects of light on human alertness, as indexed by reduced subjective sleepiness and EEG activation, are relatively consistent across studies (Cajochen et al. 2010), its effects on performance in more specific cognitive tasks are inconsistent and depend on circadian time (i.e., night versus daylight exposure), sex, and internal state (sleep deprived versus well rested) (Campbell et al. 2023, Mahoney & Schmidt 2024).

In conclusion, the non-image-forming effects of light have a significant modulatory influence on cognitive performance, especially at night, when light is tuned to activate ipRGCs. It is very likely that the direct effects of light play an important role not necessarily via the SCN but by acting directly on brain regions responsible for the maintenance of specific cognitive performance.

DISORDERS RELATED TO THE CIRCADIAN TIMING SYSTEM

Throughout history, an understanding of time and biological rhythms has been an integral part of the medical practices of different cultures. Many ancient cultures, including the Egyptians, Greeks, Indians, and Chinese, had a sophisticated understanding of time and its relationship to health and disease, which is still preserved in traditional Chinese medicine and Ayurveda, an ancient Indian medical system (Magner & Kim 2017). For example, the ancient Greek physician Hippocrates (ca. 460–370 BC) recognized the importance of seasonal changes and environmental factors in health. He and his followers observed that the symptoms of certain diseases were more prevalent at different times of the year and emphasized the importance of these patterns in medical treatment (Dong 2011). In modern societies, technological advances over the past 200 years have increased the ability to override natural biological rhythms. However, recent findings in chronobiology and sleep research have highlighted the critical importance of adhering to our circadian rhythms for health and have led to the development of a scientific discipline, chronomedicine, which explores the complex interplay between biological processes and temporal patterns in various diseases. Chronomedicine is primarily concerned with the pathologies of the circadian timing system and aims to develop, evaluate, and implement evidence-based, personalized interventions for people suffering from conditions or diseases that either result from or are associated with circadian dysfunction.

Circadian dysfunction often results in circadian rhythm sleep/wake disorders—sleep patterns that are either too early (advanced), too late (delayed), shifting daily (non-24-hour), or irregular, not aligned with personal or social schedules. Jet lag and shift work disorders are additional types, mainly due to social factors (Meyer et al. 2022). In addition to sleep problems, circadian misalignment can lead to adverse metabolic and cardiovascular effects (Scheer et al. 2009) and an increased risk of mental health problems (Walker et al. 2020) (**Figure 5**).

Impact on Mental Disorders

Given the pivotal role of neurotransmitter balance in mental health, the regulation of these neurotransmitters by the circadian timing system is emerging as a critical factor in the development of mental disorders (Walker et al. 2020, Wulff et al. 2010). Clinical studies, for example, show that the severity of major depressive disorder (MDD) correlates with the degree of disruption of circadian rhythms, and that circadian patterns of gene expression in the postmortem brains of patients with MDD show reduced amplitude, shifted peaks, and altered phase relationships (for a review, see Walker et al. 2020).

The cyclical nature of disorders such as seasonal affective disorder and bipolar disorder, alterations in the circadian and diurnal patterns of hormones such as melatonin and cortisol, disrupted rest/activity rhythms, and impaired sleep quality highlight the influence of the circadian system in both affective and psychotic mental disorders (i.e., MDD, bipolar disorder, and schizophrenia; Bromundt et al. 2011, Wulff et al. 2010). Furthermore, the requirement for circadian entrainment by external factors, often impaired in mental illness, underscores the importance of circadian alignment for mental and physical health. While these symptoms are not exclusive to any single psychiatric disorder, the efficacy of chronotherapeutic treatments highlights the circadian timing system as a valuable adjunctive target in psychiatric drug therapy (McCarthy et al. 2022, Wirz-Justice & Benedetti 2020), sometimes leading to sustained therapy success (Garbazza et al. 2022). Moreover, drugs commonly used in the treatment of mental disorders, such as lithium, sodium valproate, serotonin reuptake inhibitors, melatonin agonists, and others, may exert their effects through interactions with the circadian system, although the mechanisms are not yet fully understood (Meyer & Matt 2022). Thus, there is mounting evidence that circadian disruption is a common underlying psychopathology factor that bridges across mental disorders (Alachkar et al. 2022).

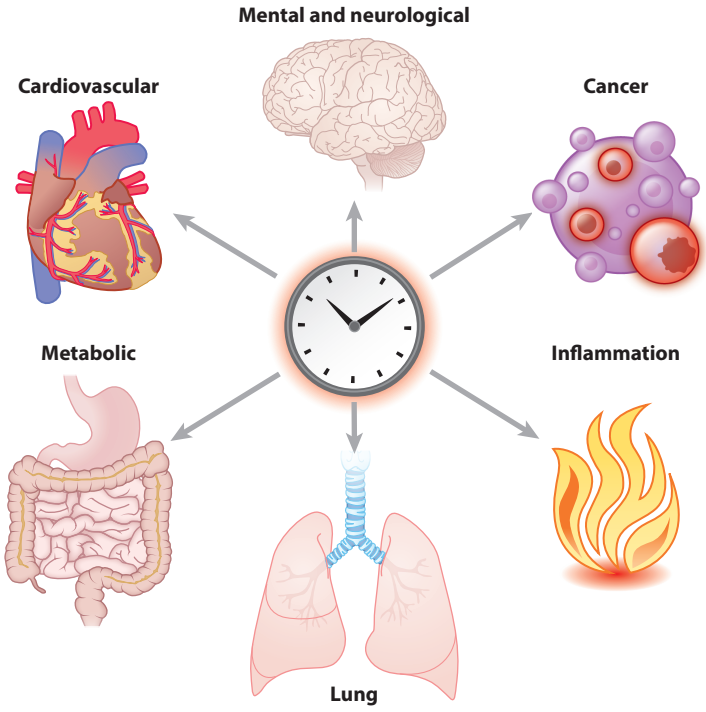

Figure 5

Circadian health emphasizes the vital role of aligning biological rhythms with natural light/dark cycles in the prevention and treatment of various mental and somatic disorders. This involves synchronizing physiological processes, including sleep/wake cycles, hormone release, and metabolism, with environmental cues. Research shows that disruption of circadian rhythms can have a significant impact on mental health, contributing to conditions such as depression, anxiety, and bipolar disorder. Additionally, circadian rhythm disturbances have been associated with neurological disorders like Parkinson's disease and Alzheimer's disease as well as metabolic conditions such as diabetes and obesity, along with somatic diseases like rheumatoid arthritis, asthma, and cardiovascular disease.

Future research should focus on functional links between circadian clock components and the biochemical pathways that control the synthesis and degradation of neurotransmitters implicated in mental disorders, particularly dopamine, which is under circadian control, while serotonin and norepinephrine may be indirectly regulated by the clock (Albrecht 2023). In addition, there is a lack of knowledge about the relationship between circadian disruption and mental disorders, from the perspective of gene expression and brain circuitry to broader investigations of whole-organism behaviors such as rest/activity cycles, sleep, and cognition to population-wide research (Meyer et al. 2024).

Impact on Neurological Disorders

While the link between the circadian timing system and mental illness has been studied for some time, it is only more recently that research has focused on neurological diseases, in particular Alzheimer's and Parkinson's dementia as well as epilepsy, all of which share many clinical symptoms that show diurnal and nocturnal variations in frequency and intensity (Karoly et al. 2021, Shen et al. 2023, Videnovic & Golombek 2013, Videnovic et al. 2014).

A large prospective study found, for example, that disrupted daily activity rhythms in older adults increase the risk of Alzheimer's dementia and accelerate the shift from mild cognitive

impairment to Alzheimer's disease (AD), underscoring a bidirectional link between circadian dysregulation and cognitive decline (Li et al. 2020). In the same vein, the brainstem LC (Van Egroo et al. 2022) and hypothalamic sleep- and wake-regulating neurons (Lew et al. 2021) have been put forward as a potential interface through which early onset of neurodegenerative and/or AD-related pathophysiological processes is associated with sleep/wake dysregulation. Accordingly, postmortem findings recently found an association between actimetry-derived 24-hour rest/activity rhythms, cognitive decline, and postmortem LC hypopigmentation in the context of AD (Van Egroo et al. 2024). Furthermore, a study explored the possibility of a causal relationship through Mendelian randomization. The results indicated that while sleep efficiency was associated with a reduced risk of AD, daytime sleepiness was associated with an increased risk of amyotrophic lateral sclerosis (Cullell et al. 2021).

Initial studies with chronotherapeutic approaches such as light therapy and the use of melatonin as a chronobiotic have shown positive results indirectly assessed through improvements in mood, daytime somnolence, and global cognitive status as measured by the Mini-Mental State Examination (MMSE) (Riemersma-van der Lek et al. 2008, Shen et al. 2023, Videnovic et al. 2017). This means that by stabilizing the circadian axis, an improvement in sleep and quality of life has been achieved in these patients. Moreover, simple bright light therapy during the day in nursing homes not only improved the regularity of the sleep/wake rhythm of residents, most of whom had dementia, but also delayed cognitive decline in this group of patients compared with patients who did not receive such treatment in a randomized clinical trial (RCT). The success of light therapy in slowing cognitive decline in this RCT was comparable to that of drug treatment (i.e., acetylcholinesterase inhibitors) (Riemersma-van der Lek et al. 2008). Promising results with light therapy have also been reported in a randomized clinical trial of Parkinson's disease patients who were treated with morning light and found that they were more alert throughout the day, had better sleep quality, and also showed improvements in motor symptoms (Videnovic et al. 2017). However, a recent meta-analysis suggests that future RCTs are needed that standardize light therapy protocols and enroll more patients to determine whether a significant therapeutic benefit has been achieved (Huang et al. 2021).

A possible link between circadian rhythms and epilepsy has long been known, as the classification of epilepsy into diurnal and nocturnal seizures goes back over 3,000 years (Karoly et al. 2021). The Babylonians classified epilepsy as either diurnal or nocturnal, according to a translation of a cuneiform text on epilepsy (Wilson & Reynolds 1990). However, it is only with the development of fully implantable EEG systems that continuous monitoring of epileptic brain activity over months or even years has become possible, opening up the possibility of identifying robust cyclical patterns in seizure occurrence that manifest themselves over long periods of time (Karoly et al. 2021). Cycles of epileptic brain activity exist on multiple timescales, including circadian, multi-day, and circannual profiles, providing the possibility of predicting seizures over long periods of time (Baud et al. 2018). In at least 80% of the 1,118 patients analyzed in the SeizureTracker data set, Karoly and colleagues were able to show that a 24-hour rhythm was present (reviewed in Karoly et al. 2021). The question remains of whether these 24-hour cycles are modulated by the SCN or reflect diurnal patterns in response to sleep/wake cycles (Khan et al. 2018). To distinguish between circadian and sleep/wake homeostasis effects at seizure occurrence, either FD or CR protocols should be used. Indeed, circadian rhythms in interictal epileptiform discharges have been reported in a study in which five patients with generalized epilepsy underwent an FD protocol in which sleep and circadian modulation were disentangled (Pavlova et al. 2009). Key unresolved issues in epilepsy research include understanding the mechanistic basis of seizure cycles and their potential clinical applications, such as chronotherapy (Karoly et al. 2021). Improved diurnal seizure prediction may allow personalized antiepileptic drug dosing synchronized with

circadian rhythms, with the potential to improve seizure control while reducing side effects and risks (Khan et al. 2018).

Implications for Other Disorders

Circadian rhythms tightly regulate metabolic, cardiovascular, and digestive functions. Disruptions to these rhythms, often due to factors like shift work or irregular sleep, can increase risk of occurrence of various other disorders (**Figure 5**). For instance, disturbances in circadian rhythms are associated with metabolic issues such as obesity and type 2 diabetes (Sato & Sato 2023); cardiovascular diseases like hypertension and stroke (Crnko et al. 2019); digestive disorders such as gastroesophageal reflux disease, irritable bowel syndrome, and inflammatory bowel disease (Zhang & Liu 2023); and inflammatory disorders such as rheumatoid arthritis (Buttgereit et al. 2015). Furthermore, circadian rhythm disruption and circadian core clock gene alterations promote cancer initiation, while the circadian clock controls several cancer hallmarks. Conversely, oncogenic processes directly weaken circadian rhythms (Sulli et al. 2019).

Circadian timing of chemotherapy may increase efficacy and reduce side effects in cancer patients; circadian timing of cardiovascular and asthma medications may lead to better outcomes in heart disease and improved lung function and symptom control; and chronomodulated drug release would further counteract the proinflammatory cytokines that contribute to the early morning joint inflammation that characterizes rheumatoid arthritis (Ballesta et al. 2017, Ruan et al. 2021).

FUTURE ISSUES

1. We are time: The importance of circadian biology is underestimated in studies of human cognitive function and has rarely been considered in preclinical studies, and even less so in translations to the bedside. Although many authors may claim to have controlled for time effects in their studies, a measure of circadian time has rarely been implemented. Circadian time is not clock time and should become the fourth dimension to be considered in preclinical studies and their translations to the bedside.
2. We need mechanisms: A more mechanistic understanding of how circadian time affects cognitive function is never enough. Current evidence from fMRI studies suggests the implication of arousal-promoting brain centers in circadian performance modulation. They further provide evidence that regional brain responses and potentially also functional networks underlying attention performance (e.g., bottom-up versus top-down processing) vary over the 24-hour cycle. Although it is difficult to dissect the underlying brain mechanisms in human studies, manipulation of the circadian timing system by light and nonphotic Zeitgebers, such as meal timing and physical activity, may at least allow us to disentangle how important individual circadian Zeitgebers are for cognitive function. The recent advent of ultrahigh-field magnetic resonance imaging (UHF MRI) opens access to new spatial scales, with functional studies directly linked to structural observations at the submillimeter scale. In the future, UHF MRI may allow finer-grained structural assessment of subcortical integrity in vivo and of its association with fluctuations in neurobehavioral performance in humans. We also need a more mechanistic understanding from a cognitive perspective: The influences of the circadian clock on specific cognitive processes remain largely unexplored (e.g., examining the circadian influence on the creation of a memory trace, from encoding through consolidation to retrieval).

3. We need to get out of the lab: Over the past 30 years, well-controlled laboratory studies in carefully selected volunteers have provided invaluable evidence to support models of human sleep/wake regulation and cognitive function within a circadian framework. Some of these findings are being translated into treatments for circadian sleep/wake disorders and into a better understanding of cognitive decline rates, for example, in Alzheimer's disease. However, much of the evidence from the laboratory needs to be taken out of the laboratory to be proven. We are only beginning to understand how major environmental changes such as the climate crisis interact with biological systems, including our circadian biology. We therefore need to integrate the environmental and psychological aspects of an individual into the design and interpretation of experimental field studies to produce more ecologically valid results. Here, physiology-based modeling can help move from lab experiments to real-world situations by checking if lab-tuned parameters work for real-world observations.
4. We need to standardize: There is a need for standardization in the quantification of circadian time and temporal organization in cognitive function. Although there is an emerging consensus on tests to measure specific aspects of human cognition (e.g., sustained attention, working memory), there is still a lack of standardized operating procedures for measuring circadian time in the field. As modern wearable technology is well suited to measuring sleep/wake behavior, it would be important to implement such a novel circadian marker in wearable trackers—for example, based on heart rate and skin temperature variables as a proxy for circadian phase.
5. We differ: Researchers in all fields are using more balanced groups and paying closer attention to sex and age differences in their findings. However, most human circadian studies have a selection bias such that most of the knowledge about how circadian and sleep/wake homeostasis modulate human cognitive function has come from above-average educated volunteers (mostly, students in the case of young samples) from industrialized societies and often preselected for being good sleepers. In addition to age and sex, we need to increase the diversity of our study volunteers by including, for example, different levels of education, mental status, and social environment, as these reflect key regulators of brain function.

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LITERATURE CITED

Achermann P, Dijk DJ, Brunner DP, Borbely AA. 1993. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. *Brain Res. Bull.* 31(1–2):97–113

Aeschbach D, Cajochen C, Landolt H, Borbely AA. 1996. Homeostatic sleep regulation in habitual short sleepers and long sleepers. *Am. J. Physiol.* 270(1 Pt. 2):R41–53

Alachkar A, Lee J, Asthana K, Vakil Monfared R, Chen J, et al. 2022. The hidden link between circadian entropy and mental health disorders. *Transl. Psychiatry* 12(1):281

Albrecht U. 2012. Timing to perfection: the biology of central and peripheral circadian clocks. *Neuron* 74(2):246–60

Albrecht U. 2023. The circadian system and mood related behavior in mice. *Adv. Protein Chem. Struct. Biol.* 137:269–91

Arble DM, Bass J, Behn CD, Butler MP, Challet E, et al. 2015. Impact of sleep and circadian disruption on energy balance and diabetes: a summary of workshop discussions. *Sleep* 38(12):1849–60

Archer SN, Schmidt C, Vandewalle G, Dijk D-J. 2018. Phenotyping of PER3 variants reveals widespread effects on circadian preference, sleep regulation, and health. *Sleep Med. Rev.* 40:109–26

Aston-Jones G. 2005. Brain structures and receptors involved in alertness. *Sleep Med.* 6(Suppl. 1):S3–7

Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. 2001. A neural circuit for circadian regulation of arousal. *Nat. Neurosci.* 4(7):732–38

Ballesta A, Innominato PF, Dallmann R, Rand DA, Levi FA. 2017. Systems chronotherapeutics. *Pharmacol. Rev.* 69(2):161–99

Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, et al. 2018. Multi-day rhythms modulate seizure risk in epilepsy. *Nat. Commun.* 9(1):88

Belle MD. 2015. Circadian tick-talking across the neuroendocrine system and suprachiasmatic nuclei circuits: the enigmatic communication between the molecular and electrical membrane clocks. *J. Neuroendocr.* 27(7):567–76

Blatter K, Cajochen C. 2007. Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. *Physiol. Behav.* 90(2–3):196–208

Blatter K, Opwis K, Munch M, Wirz-Justice A, Cajochen C. 2005. Sleep loss-related decrements in planning performance in healthy elderly depend on task difficulty. *J. Sleep Res.* 14(4):409–17

Borbély AA. 1982. A two process model of sleep regulation. *Hum. Neurobiol.* 1(3):195–204

Borbély AA, Acherman P. 2005. Sleep homeostasis and models of sleep regulation. In *Principles and Practices of Sleep Medicine*, ed. MH Kryger, T Roth, WC Dement, pp. 405–18. St. Louis, MO: Elsevier Saunders

Bromundt V, Koster M, Georgiev-Kill A, Opwis K, Wirz-Justice A, et al. 2011. Sleep-wake cycles and cognitive functioning in schizophrenia. *Br. J. Psychiatry* 198(4):269–76

Buijs RM, Kalsbeek A. 2001. Hypothalamic integration of central and peripheral clocks. *Nat. Rev. Neurosci.* 2(7):521–26

Burke TM, Scheer FAJL, Ronda JM, Czeisler CA, Wright KP Jr. 2015. Sleep inertia, sleep homeostatic and circadian influences on higher-order cognitive functions. *J. Sleep Res.* 24(4):364–71

Burki T. 2017. Nobel Prize awarded for discoveries in circadian rhythm. *Lancet* 390(10104):e25

Buttgereit F, Smolen JS, Coogan AN, Cajochen C. 2015. Clocking in: chronobiology in rheumatoid arthritis. *Nat. Rev. Rheumatol.* 11(6):349–56

Cajochen C. 2007. Alerting effects of light. *Sleep Med. Rev.* 11(6):453–64

Cajochen C, Chellappa S, Schmidt C. 2010. What keeps us awake? The role of clocks and hourglasses, light, and melatonin. *Int. Rev. Neurobiol.* 93:57–90

Cajochen C, Khalsa SB, Wyatt JK, Czeisler CA, Dijk DJ. 1999. EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *Am. J. Physiol.* 277(3 Pt. 2):R640–49

Cajochen C, Knoblauch V, Wirz-Justice A, Krauchi K, Graw P, Wallach D. 2004. Circadian modulation of sequence learning under high and low sleep pressure conditions. *Behav. Brain Res.* 151(1–2):167–76

Campbell I, Sharifpour R, Vandewalle G. 2023. Light as a modulator of non-image-forming brain functions—positive and negative impacts of increasing light availability. *Clocks Sleep* 5(1):116–40

Carskadon MA, Dement WC. 1975. Sleep studies on a 90-minute day. *Electroencephalogr. Clin. Neurophysiol.* 39(2):145–55

Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J. 2003. Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *J. Neurosci.* 23(33):10691–702

Cohen DA, Wang W, Klerman EB, Rajaratnam SMW. 2010. Ramelteon prior to a short evening nap impairs neurobehavioral performance for up to 12 hours after awakening. *J. Clin. Sleep Med.* 6(6):565–71

Cohen RA, Albers HE. 1991. Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: a case study. *Neurology* 41(5):726–29

Crnko S, Du Pre BC, Sluijter JPG, Van Laake LW. 2019. Circadian rhythms and the molecular clock in cardiovascular biology and disease. *Nat. Rev. Cardiol.* 16(7):437–47

Cullell N, Carcel-Marquez J, Gallego-Fabrega C, Muino E, Llucia-Carol L, et al. 2021. Sleep/wake cycle alterations as a cause of neurodegenerative diseases: a Mendelian randomization study. *Neurobiol. Aging* 106:320.e1–e12

Czeisler CA, Zimmerman JC, Ronda JM, Moore-Ede MC, Weitzman ED. 1980. Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. *Sleep* 2(3):329–46

Daan S, Beersma DGM, Borbély AA. 1984. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.* 246:R161–78

Deboer T, Vansteensel MJ, Detari L, Meijer JH. 2003. Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat. Neurosci.* 6(10):1086–90

DelRosso LM, Hoque R, James S, Gonzalez-Toledo E, Chesson AL Jr. 2014. Sleep-wake pattern following gunshot suprachiasmatic damage. *J. Clin. Sleep Med.* 10(4):443–45

Deurveilher S, Semba K. 2005. Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: implications for the circadian control of behavioural state. *Neuroscience* 130(1):165–83

Dijk DJ, Czeisler CA. 1994. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci. Lett.* 166(1):63–68

Dijk DJ, Czeisler CA. 1995. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves and sleep spindle activity in humans. *J. Neurosci.* 15:3526–38

Dijk DJ, Duffy JF, Czeisler CA. 1992. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J. Sleep Res.* 1(2):112–17

Dijk DJ, Shanahan TL, Duffy JF, Ronda JM, Czeisler CA. 1997. Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *J. Physiol.* 505(Pt. 3):851–58

Dijk DJ, von Schantz M. 2005. Timing and consolidation of human sleep, wakefulness, and performance by a symphony of oscillators. *J. Biol. Rhythm* 20(4):279–90

Dong Q. 2011. Seasonal changes and seasonal regimen in Hippocrates. *J. Cambridge Stud.* 6(4):128–44

Duffy JF, Dijk DJ, Hall EF, Czeisler CA. 1999. Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. *J. Investig. Med.* 47(3):141–50

Duffy JF, Rimmer DW, Czeisler CA. 2001. Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behav. Neurosci.* 115(4):895–99

Ebbinghaus H. 1913 (1885). *Memory: A Contribution to Experimental Psychology*. New York: Teach. Coll. Columbia Univ.

Edgar DM, Dement WC, Fuller CA. 1993. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J. Neurosci.* 13(3):1065–79

Folkard S, Knauth P, Monk TH. 1976. The effect of memory load on the circadian variation in performance efficiency under a rapidly rotating shift system. *Ergonomics* 19(4):479–88

Folkard S, Totterdell P. 1994. "Time since sleep" and "body clock" components of alertness and cognition. *Acta Psychiatr. Belg.* 94(2):73–74

Francois M, Delgado IC, Lafond A, Lewis EM, Kuromaru M, et al. 2023. Amygdala AVPR1A mediates susceptibility to chronic social isolation in females. bioRxiv 2023.02.15.528679

Frank MG, Cantera R. 2014. Sleep, clocks, and synaptic plasticity. *Trends Neurosci.* 37(9):491–501

Franken P, Dijk D-J. 2024. Sleep and circadian rhythmicity as entangled processes serving homeostasis. *Nat. Rev. Neurosci.* 25(1):43–59

Frey DJ, Badia P, Wright KP Jr. 2004. Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. *J. Sleep Res.* 13(4):305–15

Garbazza C, Cirignotta F, D'Agostino A, Cicolin A, Hackethal S, et al. 2022. Sustained remission from perinatal depression after bright light therapy: a pilot randomised, placebo-controlled trial. *Acta Psychiatr. Scand.* 146(4):350–56

Gitelman DR. 2003. Attention and its disorders. *Br. Med. Bull.* 65:21–34

Grady S, Aeschbach D, Wright KPJ, Czeisler CA. 2010. Effect of modafinil on impairments in neurobehavioral performance and learning associated with extended wakefulness and circadian misalignment. *Neuropsychopharmacology* 35(9):1910–20

Groeger JA, Viola AU, Lo JC, von Schantz M, Archer SN, Dijk DJ. 2008. Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. *Sleep* 31(8):1159–67

Harrington ME, Rusak B. 1989. Photic responses of geniculo-hypothalamic tract neurons in the Syrian hamster. *Vis. Neurosci.* 2(4):367–75

Hastings MH, Maywood ES, Brancaccio M. 2019. The mammalian circadian timing system and the suprachiasmatic nucleus as its pacemaker. *Biology* 8(1):13

Horowitz TS, Cade BE, Wolfe JM, Czeisler CA. 2003. Searching night and day: a dissociation of effects of circadian phase and time awake on visual selective attention and vigilance. *Psychol. Sci.* 14(6):549–57

Huang HT, Huang TW, Hong CT. 2021. Bright light therapy for Parkinson disease: a literature review and meta-analysis of randomized controlled trials. *Biology* 10(11):1205

Huber R, Ghilardi MF, Massimini M, Tononi G. 2004. Local sleep and learning. *Nature* 430(6995):78–81

Hull JT, Wright KP Jr., Czeisler CA. 2003. The influence of subjective alertness and motivation on human performance independent of circadian and homeostatic regulation. *J. Biol. Rhythm.* 18(4):329–38

Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, Czeisler CA. 1992. Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *J. Sleep Res.* 1(1):24–29

Kalsbeek A, Yi CX, Cailotto C, la Fleur SE, Fliers E, Buijs RM. 2011. Mammalian clock output mechanisms. *Essays Biochem.* 49(1):137–51

Karoly PJ, Rao VR, Gregg NM, Worrell GA, Bernard C, et al. 2021. Cycles in epilepsy. *Nat. Rev. Neurol.* 17(5):267–84

Khalsa SB, Jewett ME, Cajochen C, Czeisler CA. 2003. A phase response curve to single bright light pulses in human subjects. *J. Physiol.* 549(3):945–52

Khan S, Nobili L, Khatami R, Loddenkemper T, Cajochen C, et al. 2018. Circadian rhythm and epilepsy. *Lancet Neurol.* 17(12):1098–108

Killgore WDS. 2010. Effects of sleep deprivation on cognition. *Prog. Brain Res.* 185:105–29

Kleitman N, Titelbaum S, Feiveson P. 1938. The effect of body temperature on reaction time. *Am. J. Physiol.* 121:495–501

Krueger JM, Nguyen JT, Dykstra-Aiello CJ, Taishi P. 2019. Local sleep. *Sleep Med. Rev.* 43:14–21

Kyriacou CP, Hastings MH. 2010. Circadian clocks: genes, sleep, and cognition. *Trends Cogn. Sci.* 14(6):259–67

Lavie P. 1986. Ultrashort sleep-waking schedule. III. "Gates" and "forbidden zones" for sleep. *Electroencephalogr. Clin. Neurophysiol.* 63(5):414–25

Lavie P. 2001. Sleep-wake as a biological rhythm. *Annu. Rev. Psychol.* 52:277–303

Lazar AS, Lazar ZI, Dijk D-J. 2015. Circadian regulation of slow waves in human sleep: topographical aspects. *NeuroImage* 116:123–34

Lew CH, Petersen C, Neylan TC, Grinberg LT. 2021. Tau-driven degeneration of sleep- and wake-regulating neurons in Alzheimer's disease. *Sleep Med. Rev.* 60:101541

Li P, Gao L, Gaba A, Yu L, Cui L, et al. 2020. Circadian disturbances in Alzheimer's disease progression: a prospective observational cohort study of community-based older adults. *Lancet Heal. Longev.* 1(3):e96–105

Lim J, Dinges DF. 2010. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol. Bull.* 136(3):375–89

Lo JC, Groeger JA, Santhi N, Arbon EL, Lazar AS, et al. 2012. Effects of partial and acute total sleep deprivation on performance across cognitive domains, individuals and circadian phase. *PLOS ONE* 7(9):e45987

Ly JQM, Gaggioni G, Chellappa SL, Papachilleos S, Brzozowski A, et al. 2016. Circadian regulation of human cortical excitability. *Nat. Commun.* 7:11828

Ma N, Dinges DF, Basner M, Rao H. 2015. How acute total sleep loss affects the attending brain: a meta-analysis of neuroimaging studies. *Sleep* 38(2):233–40
Magner LN, Kim O. 2017. *A History of Medicine*. Boca Raton, FL: CRC Press. 3rd ed.
Mahoney HL, Schmidt TM. 2024. The cognitive impact of light: illuminating ipRGC circuit mechanisms. *Nat. Rev. Neurosci.* 25(3):159–75
Maire M, Reichert CF, Gabel V, Viola AU, Phillips C, et al. 2015. Fighting sleep at night: brain correlates and vulnerability to sleep loss. *Ann. Neurol.* 78(2):235–47
Maire M, Reichert CF, Gabel V, Viola AU, Phillips C, et al. 2018. Human brain patterns underlying vigilant attention: impact of sleep debt, circadian phase and attentional engagement. *Sci. Rep.* 8(1):970
McCarthy MJ, Gottlieb JF, Gonzalez R, McClung CA, Alloy LB, et al. 2022. Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: a critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology. *Bipolar Disord.* 24(3):232–63
Meyer C, Muto V, Jaspar M, Kussé C, Lambot E, et al. 2016. Seasonality in human cognitive brain responses. *PNAS* 113(11):3066–71
Meyer N, Harvey AG, Lockley SW, Dijk DJ. 2022. Circadian rhythms and disorders of the timing of sleep. *Lancet* 400(10357):1061–78
Meyer N, Lok R, Schmidt C, Kyle SD, McClung CA, et al. 2024. The sleep-circadian interface: a window into mental disorders. *PNAS* 121(9):e2214756121
Meyer N, Matt J. 2022. *Sleep, circadian rhythms and mental health: advances, gaps, challenges and opportunities.* Rep. Summ., Wellcome Trust, London
Mistlberger RE. 2005. Circadian regulation of sleep in mammals: role of the suprachiasmatic nucleus. *Brain Res. Rev.* 49(3):429–54
Mistlberger RE, Skene DJ. 2005. Nonphotic entrainment in humans? *J. Biol. Rhythm.* 20(4):339–52
Mongrain V, Carrier J, Dumont M. 2006. Difference in sleep regulation between morning and evening circadian types as indexed by antero-posterior analyses of the sleep EEG. *Eur. J. Neurosci.* 23(2):497–504
Moore RY. 2013. The suprachiasmatic nucleus and the circadian timing system. *Prog. Mol. Biol. Transl. Sci.* 119:1–28
Morin LP. 2013. Neuroanatomy of the extended circadian rhythm system. *Exp. Neurol.* 243:4–20
Muto V, Jaspar M, Meyer C, Kusse C, Chellappa SL, et al. 2016. Local modulation of human brain responses by circadian rhythmicity and sleep debt. *Science* 353(6300):687–90
Ono D, Weaver DR, Hastings MH, Honma KI, Honma S, Silver R. 2024. The suprachiasmatic nucleus at 50: looking back, then looking forward. *J. Biol. Rhythm.* 39(2):135–65
Pavlova MK, Shea SA, Scheer FA, Bromfield EB. 2009. Is there a circadian variation of epileptiform abnormalities in idiopathic generalized epilepsy? *Epilepsy Behav.* 16(3):461–67
Pittendrigh CS. 1993. Temporal organization: reflections of a Darwinian clock-watcher. *Annu. Rev. Physiol.* 55:16–54
Portas CM, Rees G, Howseman AM, Josephs O, Turner R, Frith CD. 1998. A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *J. Neurosci.* 18(21):8979–89
Postnova S. 2019. Sleep modelling across physiological levels. *Clocks Sleep* 1(1):166–84
Reichert CF, Maire M, Gabel V, Viola AU, Götz T, et al. 2017. Cognitive brain responses during circadian wake-promotion: evidence for sleep-pressure-dependent hypothalamic activations. *Sci. Rep.* 7(1):5620
Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. 2008. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA* 299(22):2642–55
Roenneberg T, Daan S, Merrow M. 2003. The art of entrainment. *J. Biol. Rhythm.* 18(3):183–94
Rosenberg J, Pusch K, Dietrich R, Cajochen C. 2009. The tick-tock of language: Is language processing sensitive to circadian rhythmicity and elevated sleep pressure? *Chronobiol. Int.* 26(5):974–91
Ruan W, Yuan X, Eltzschig HK. 2021. Circadian rhythm as a therapeutic target. *Nat. Rev. Drug Discov.* 20(4):287–307
Santhi N, Lazar AS, McCabe PJ, Lo JC, Groeger JA, Dijk D-J. 2016. Sex differences in the circadian regulation of sleep and waking cognition in humans. *PNAS* 113(19):E2730–39

Sato T, Sato S. 2023. Circadian regulation of metabolism: commitment to health and diseases. *Endocrinology* 164(7):bqad086

Scammell TE, Arrigoni E, Lipton JO. 2017. Neural circuitry of wakefulness and sleep. *Neuron* 93(4):747–65

Scheer FA, Hilton MF, Mantzoros CS, Shea SA. 2009. Adverse metabolic and cardiovascular consequences of circadian misalignment. *PNAS* 106(11):4453–58

Schmidt C, Collette F, Cajochen C, Peigneux P. 2007. A time to think: circadian rhythms in human cognition. *Cogn. Neuropsychol.* 24(7):755–89

Schmidt C, Collette F, Leclercq Y, Sterpenich V, Vandewalle G, et al. 2009. Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area. *Science* 324(5926):516–19

Schmidt C, Collette F, Reichert CF, Maire M, Vandewalle G, et al. 2015. Pushing the limits: Chronotype and time of day modulate working memory-dependent cerebral activity. *Front. Neurol.* 6:199

Schmidt C, Peigneux P, Leclercq Y, Sterpenich V, Vandewalle G, et al. 2012. Circadian preference modulates the neural substrate of conflict processing across the day. *PLOS ONE* 7(1):e29658

Schmidt TM, Do MT, Dacey D, Lucas R, Hattar S, Matynia A. 2011. Melanopsin-positive intrinsically photosensitive retinal ganglion cells: from form to function. *J. Neurosci.* 31(45):16094–101

Schöllhorn I, Stefani O, Lucas RJ, Spitschan M, Slawik HC, Cajochen C. 2023. Melanopic irradiance defines the impact of evening display light on sleep latency, melatonin and alertness. *Commun. Biol.* 6(1):228

Shekleton JA, Rajaratnam SMW, Gooley JJ, Van Reen E, Czeisler CA, Lockley SW. 2013. Improved neurobehavioral performance during the wake maintenance zone. *J. Clin. Sleep Med.* 9(4):353–62

Shen Y, Lv QK, Xie WY, Gong SY, Zhuang S, et al. 2023. Circadian disruption and sleep disorders in neurodegeneration. *Transl. Neurodegener.* 12(1):8

Silva EJ, Wang W, Ronda JM, Wyatt JK, Duffy JF. 2010. Circadian and wake-dependent influences on subjective sleepiness, cognitive throughput, and reaction time performance in older and young adults. *Sleep* 33(4):481–90

Späti J, Aritake S, Meyer AH, Kitamura S, Hida A, et al. 2015. Modeling circadian and sleep-homeostatic effects on short-term interval timing. *Front. Integr. Neurosci.* 9:15

Späti J, Münch M, Blatter K, Knoblauch V, Jones LA, Cajochen C. 2009. Impact of age, sleep pressure and circadian phase on time-of-day estimates. *Behav. Brain Res.* 201(1):48–52

Sprecher KE, Ritchie HK, Burke TM, Depner CM, Smits AN, et al. 2019. Trait-like vulnerability of higher-order cognition and ability to maintain wakefulness during combined sleep restriction and circadian misalignment. *Sleep* 42(8):zsz113

Starnes AN, Jones JR. 2023. Inputs and outputs of the mammalian circadian clock. *Biology* 12(4):508

Strogatz SH, Kronauer RE, Czeisler CA. 1987. Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia. *Am. J. Physiol.* 253(1 Pt. 2):R172–78

Sulli G, Lam MTY, Panda S. 2019. Interplay between circadian clock and cancer: new frontiers for cancer treatment. *Trends Cancer* 5(8):475–94

Tucker AM, Stern Y, Basner RC, Rakitin BC. 2011. The prefrontal model revisited: double dissociations between young sleep deprived and elderly subjects on cognitive components of performance. *Sleep* 34(8):1039–50

Van Dongen HP, Baynard MD, Maislin G, Dinges DF. 2004. Systematic interindividual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. *Sleep* 27(3):423–33

Van Egroo M, Koshmanova E, Vandewalle G, Jacobs HIL. 2022. Importance of the locus coeruleus-norepinephrine system in sleep-wake regulation: implications for aging and Alzheimer's disease. *Sleep Med. Rev.* 62:101592

Van Egroo M, van Someren EJW, Grinberg LT, Bennett DA, Jacobs HIL. 2024. Associations of 24-hour rest-activity rhythm fragmentation, cognitive decline, and postmortem locus coeruleus hypopigmentation in Alzheimer's disease. *Ann. Neurol.* 95(4):653–64

Vandewalle G, Maquet P, Dijk DJ. 2009. Light as a modulator of cognitive brain function. *Trends Cogn. Sci.* 13(10):429–38

Videnovic A, Golombek D. 2013. Circadian and sleep disorders in Parkinson's disease. *Exp. Neurol.* 243:45–56

Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC. 2017. Timed light therapy for sleep and daytime sleepiness associated with Parkinson disease: a randomized clinical trial. *JAMA Neurol.* 74(4):411–18

Videnovic A, Lazar AS, Barker RA, Overeem S. 2014. "The clocks that time us"—circadian rhythms in neurodegenerative disorders. *Nat. Rev. Neurol.* 10(12):683–93

Viola AU, Archer SN, James LM, Groeger JA, Lo JC, et al. 2007. PER3 polymorphism predicts sleep structure and waking performance. *Curr. Biol.* 17(7):613–18

Walker WH II, Walton JC, DeVries AC, Nelson RJ. 2020. Circadian rhythm disruption and mental health. *Transl. Psychiatry* 10(1):28

Wang W, Yuan RK, Mitchell JF, Zitting K-M, St Hilaire MA, et al. 2023. Desynchronizing the sleep–wake cycle from circadian timing to assess their separate contributions to physiology and behaviour and to estimate intrinsic circadian period. *Nat. Protoc.* 18(2):579–603

Wilson JV, Reynolds EH. 1990. Texts and documents. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. *Med. Hist.* 34(2):185–98

Wirz-Justice A, Benedetti F. 2020. Perspectives in affective disorders: clocks and sleep. *Eur. J. Neurosci.* 51(1):346–65

Wright KP Jr., Hull JT, Czeisler CA. 2002. Relationship between alertness, performance, and body temperature in humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 283:R1370–77

Wright KP Jr., Hull JT, Hughes RJ, Ronda JM, Czeisler CA. 2006. Sleep and wakefulness out of phase with internal biological time impairs learning in humans. *J. Cogn. Neurosci.* 18(4):508–21

Wulff K, Gatti S, Wettstein JG, Foster RG. 2010. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat. Rev. Neurosci.* 11(8):589–99

Wyatt JK, Ritz-De Cecco A, Czeisler CA, Dijk DJ. 1999. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a 20-h day. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 277:R1152–63

Zeitzer JM, Buckmaster CL, Parker KJ, Hauck CM, Lyons DM, Mignot E. 2003. Circadian and homeostatic regulation of hypocretin in a primate model: implications for the consolidation of wakefulness. *J. Neurosci.* 23(8):3555–60

Zhang C, Liu X. 2023. Fundamental crosstalk between circadian rhythm and the intestine in the pathogenesis of inflammatory bowel disease. *Clin. Res. Hepatol. Gastroenterol.* 47(9):102214

Zhang DX, Rusak B. 1989. Photic sensitivity of geniculate neurons that project to the suprachiasmatic nuclei or the contralateral geniculate. *Brain Res.* 504(1):161–64

Zhou X, Ferguson SA, Matthews RW, Sargent C, Darwent D, et al. 2011. Sleep, wake and phase dependent changes in neurobehavioral function under forced desynchrony. *Sleep* 34(7):931–41