10. Circadian biology/Chronobiology

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Summary

Chronobiology is the science of biological rhythms, amongst which circadian rhythms with a nearly 24-hr period are the most relevant for human physiology and health. In mammals, the circadian timekeeping system is organized in a hierarchical manner, with a "master clock" in the hypothalamus receiving non-visual light inputs through specialized photoreceptors in the retina, in order to synchronize endogenous rhythms to the environmental light–dark cycle. The sleep–wake rhythm is also normally entrained through photic and non-photic Zeitgebers to the 24-hr solar day, but inter-individual variants in period length, circadian amplitude, and phase or light sensitivity characterize different chronotypes, in which sleep occurs at a different circadian phase of entrainment. However, sleep timing and structure are not only under circadian control, but are finely regulated by a complex interaction between two oscillatory processes: an hourglass-like homeostatic mechanism depending on the prior duration of sleep and wakefulness (process S) and an intrinsic 24-hr rhythm driven by the circadian pacemaker (process C). Alteration of the synergy between process S and C and disruption of internal circadian rhythms may not only lead to sleep–wake disturbances, but also be involved in the pathophysiology of several diseases, that represent the focus of research and clinical applications of circadian medicine.

KEYWORDS

biological clock, chronobiology, chronotypes, circadian medicine, circadian rhythms, circadian timing system, diurnal rhythms, intrinsically photosensitive retinal ganglion cells, light, two process model of sleep-wake regulation, melatonin, Zeitgeber

1 | THE CIRCADIAN TIMING SYSTEM

Life on earth undergoes cycles and it comes as no surprise that evolution has favoured temporal information to become incorporated in almost every living organism. The 24-hr rotation of our planet around its axis drives predictable changes in the environment, which can be anticipated by endogenous clocks. The study of temporal organization in biological systems controlled by endogenous clocks is called chronobiology. On the system levels, chronobiology covers biological rhythms over a wide range of aspects from gene regulation to complex human behaviour such as cognitive performance and mood states. From an evolutionary perspective, it makes sense that endogenous clocks help organisms prepare for daily, seasonal, monthly etc., periodic changes. Accordingly, endogenous rhythms with different periods have been observed ranging from ultradian (periods of <24 hr), to circadian (*circa diem*, period of ~24 hr; i.e., daily rhythms), to infradian rhythms (periods of >24 hr; e.g., seasonal rhythms) in cyanobacteria to humans. From all these different rhythms, the circadian timing system has drawn most attention in chronobiology research and has the potential to become part of mainstream medical education or practice. In fact, the Nobel Prize for Physiology or Medicine has been awarded to pioneers in the discovery of the molecular clockwork of circadian rhythms in 2017. In the official statement by the Nobel committee the ubiquitous importance of the circadian timing system has been acknowledged with the following statement: "the seminal discoveries by the three laureates, circadian biology has developed into a vast and highly dynamic research field, with implications for our

health and wellbeing" (https://www.nobelprize.org/prizes/medicine/2017/press-release/).

1.1 | Circadian clocks everywhere

Circadian rhythms drive fundamental aspects of cellular and physiological function in the brain and body. The main role of this intrinsic timekeeping system is to enforce a temporal architecture from the behavioural level to the metabolomic, proteomic, transcriptomic, and methylomic levels even in the absence of external cues (for a review see Buttgereit, Smolen, Coogan, & Cajochen, 2015). All of this guarantees temporal segregation of behavioural and physiological processes for an optimally timed adaptation to the environment. Intrinsic temporal organization of human biology is achieved through the integration of hierarchically organized, multi-oscillator systems via the interplay of central oscillators and their feedback from peripheral rhythms as well as from systemic, behavioural, and environmental cues. At the top of this hierarchy is the "central clock" located in the suprachiasmatic nuclei (SCN), which generate circadian rhythms in neuronal activity and peptide release, which, in turn, are important synchronizing cues to other brain and body regions (Hastings, Maywood, & Brancaccio, 2018). The central SCN clock is considered to act as a master clock that synchronizes peripheral clocks and conveys time-of-day information to peripheral organs (Figure 1). Disturbances in this coupling of central and peripheral clocks can lead to metabolic dysfunction, cardiovascular problems, and also increased cancer risk (Sulli, Lam, & Panda, 2019).

Circadian rhythms are genetically encoded. The molecular clockwork in mammals is based on interlocked transcriptional/translational feedback loops (TTFLs) turning over at a rate that approximates the solar day (Bollinger & Schibler, 2014). According to Schibler (Schibler, 2019), in the primary TTFL, the transcription factors *circadian locomotor output cycles protein kaput (CLOCK)* and *brain and muscle ARNT-like 1 (BMAL1)* activate the transcription of *Cryptochrome 1 and 2 (CRY 1, CRY 2), Period 1 and 2 (PER 1, PER 2)* The four proteins encoded by these genes are assembled into large repressor complexes (Aryal et al., 2017), which, when reaching a critical level, inhibit their own transcription. CRY and PER proteins are degraded, thus restoring *BMAL1-CLOCK* activity. The robustness of this TTFL is amplified by a secondary TTFL, in which positively and negatively acting orphan nuclear receptors of the retinoic acid receptor-related orphan receptors (RORs) and REV-ERB families, respectively, regulate the cyclic transcription of the *CLOCK* and *BMAL1* genes (Dibner, Schibler, & Albrecht, 2010). Fascinatingly, the principle of this molecular clock machinery is evolutionary well-preserved throughout the animal and plant kingdoms in order to optimally anticipate daily cycles of light–dark, temperature, and food availability. These cell-autonomous clocks throughout the brain and body are generally synchronized with each other and with the external environment, which is attained by coordination with the central SCN pacemaker and integration with environmental cues (Bollinger & Schibler, 2014).

KEY POINTS

- Circadian rhythms are self-sustained oscillations in biological or behavioural processes that show a nearly 24-hr period and are directly or indirectly controlled by circadian clocks. Clock genes are present in almost every cell and coordinate a complex regulatory network based on multiple negative and positive feedback loops.
- Photic and non-photic time signals (Zeitgebers) are essential in synchronizing endogenous circadian rhythms with cyclic environmental changes, in a process known as circadian entrainment.
- Light is the most important Zeitgeber, providing direct information about the 24-hr solar day to the master circadian clock, located in the hypothalamus, via the retina. However, light has also many other non-visual effects on human and animal behaviour, affecting alertness, cognition, mood, and sleep through different pathways.
- Timing, duration, and structure of sleep depend on the interaction between a homeostatic sleep–wake counter (process S) and an internal 24-hr rhythm in sleep–wake propensity (process C). The phase relationship between these two processes influences the stability and pattern of the sleep–wake cycle.
- Circadian medicine is a promising new field of medicine aimed at optimizing therapeutic interventions by targeting the circadian system, in order to improve overall health beyond sleep. Besides non-pharmacological chronotherapeutics, it also includes chronopharmacological approaches based on the timing of drug delivery in order to increase their efficacy and reduce side effects.

LEARNING OBJECTIVES

- Learn about the research focus of chronobiology and the hierarchical organization of the circadian system.
- Understand the concept of circadian entrainment and the role of Zeitgebers, particularly light, in synchronizing internal and external time.
- Know the main biological characteristics that differentiate early from late chronotypes.
- Comprehend how the circadian and homeostatic processes interact in the regulation of sleep and wakefulness.
- Gain knowledge about the main interests, applications, and future prospects of circadian medicine.

1.2 | Setting the circadian clock by Zeitgebers (timing cues)

Information about endogenous time, generated by the central circadian pacemaker in the SCN, is transmitted to the rest of the body via

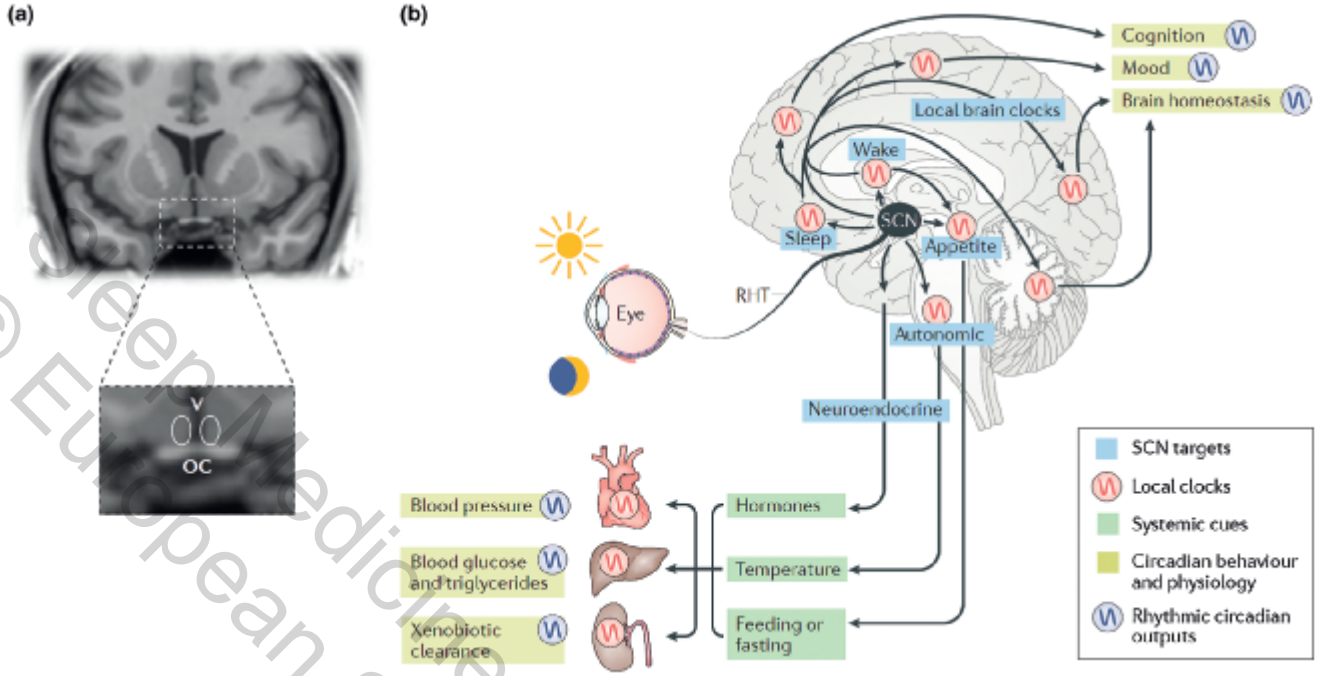

FIGURE 1 (a) The principal circadian clock, the suprachiasmatic nucleus (SCN), is located in the hypothalamus, which is highlighted by the box on the coronal magnetic resonance imaging scan of a human brain. The inset shows an enlarged view, with the location of the SCN outlined. The optic chiasm (OC) lies across the base of the midline third ventricle (V). (b) The SCN receives direct retinal innervation via the retino-hypothalamic tract (RHT) to ensure its synchronization to day–night cycles. The SCN clock projects to various brain centres, many of which contain local circadian clocks that direct behavioural (e.g., feeding–fasting and sleep–wakefulness), autonomic, and neuroendocrine circadian rhythms. These systemic cues synchronize the local molecular clocks of peripheral tissues, and these local clocks in turn direct local programmes of circadian gene expression that regulate physiological rhythms critical to health (e.g., rhythms relating to mental alertness, blood pressure, triglyceride metabolism, and renal function). With permission from (Hastings et al., 2018)

humoral factors and via the autonomic nervous system (Bollinger & Schibler, 2014). Endogenous time or *inner time* is per definition not driven by exogenous time cues or *external time*, which comprises environmental light–dark and temperature cycles, our civil time in different time zones as well as our social time (e.g., working schedules). In fact, endogenous circadian clocks do not deteriorate under complete time isolation, but tick at their own speed (e.g., period length). This period length, often called tau, differs considerably amongst humans and deviates significantly from 24 hr, on average by 0.2 hr (Czeisler et al., 1999). Thus, endogenously generated circadian time signals need environmental cyclic time signals (e.g., Zeitgebers) in order to synchronize with cyclic alterations in the environment. Circadian clocks have to be reset by a few minutes every day. This process is called circadian entrainment (Roenneberg, Wirz-Justice, & Merrow, 2003) (Figure 2). *Parametric* circadian entrainment is considered as a continuous process in which the circadian oscillator constantly accelerates and decelerates to adapt to the environment, whilst the circadian oscillator is advanced or delayed every day in an almost instantaneous manner in a *non-parametric* view of entrainment (Daan, 2000).

The most common and highly regular Zeitgeber for most organisms on Earth is the daily light–dark cycle (Roenneberg et al., 2003). Amongst different Zeitgebers, light is the most powerful also for humans, if the light–dark cycle period length is close to 24 hr with a strong enough intensity change between light and darkness. Other so called non-photic Zeitgebers, such as rest–activity cycles, meal timing, and social time are weaker in comparison to light. In fact, a complete blind person without eyes does typically not entrain her/his circadian sleep–wake rhythm to the environment, despite non-photic Zeitgebers such as for instance walking the guide dog every morning at the exact same clock time. For those people, exogenous melatonin as a non-photic Zeitgeber may replace the photic Zeitgeber light (Sack & Lewy, 1997). Many studies showed that timed melatonin administration can help entraining totally blind people (Skene & Arendt, 2007; Skene, Lockley, & Arendt, 1999). In addition, circadian phase advances after melatonin administration in the early evening have been reported also for sighted people (Kräuchi, Cajochen, Möri, Graw, & Wirz-Justice, 1997), whilst clear phase delays were not observed (Burgess, Revell, Molina, & Eastman, 2010). As melatonin also has soporific properties and attenuates circadian wake promotion in the evening (Cajochen, Kräuchi, & Wirz-Justice, 1997), it is recommended in the evening for people with a delayed sleep phase syndrome in combination with light treatment in the morning. Scheduled exposure to light or avoidance of light in combination with timed melatonin administration, both scheduled according to the phase response curve for light and melatonin (Figure 3), is the most often used chronotherapeutic treatment to re-align patients who show impaired circadian

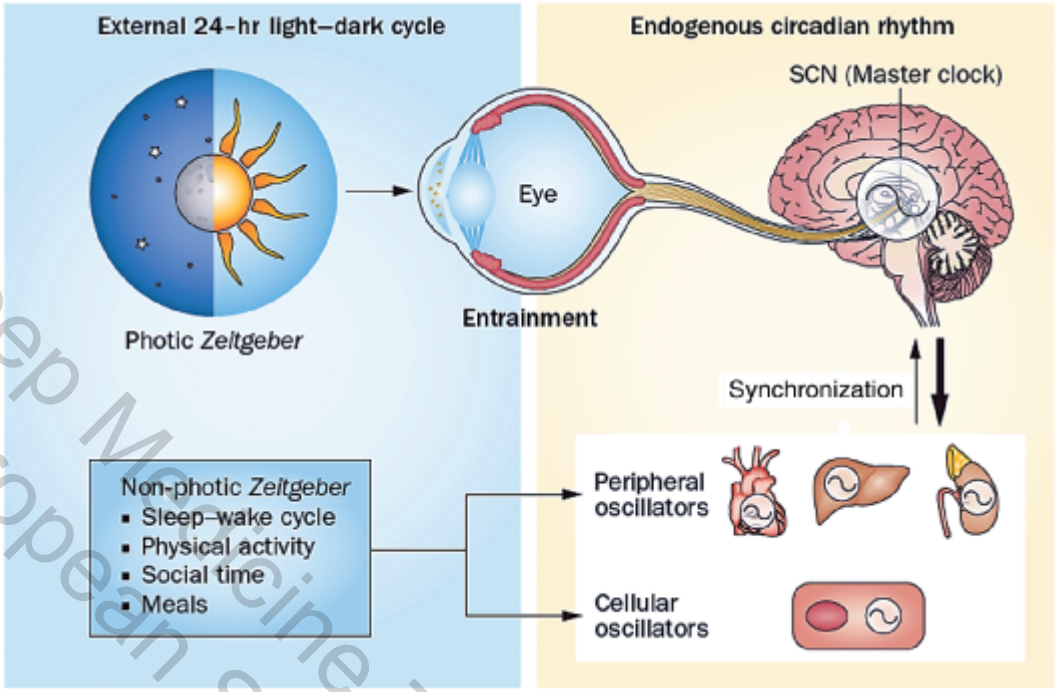

FIGURE 2 Intrinsic circadian oscillations in the brain (SCN) and the periphery (organs) are synchronized via humoral signals and the autonomic nervous system. The circadian system actively synchronizes the temporal sequence of biological functions with the environment. The light–dark cycle is the most important Zeitgeber (synchronizer). Other potential environmental entrainment cues stem from sleep–wake and activity cycles, meal timing, and societal rhythms such as work and leisure times. SCN, suprachiasmatic nuclei (with permission from Buttgereit et al., 2015)

entrainment (i.e., circadian rhythms are not in optimal synchrony with the ambient light–dark cycle).

The role of non-photic Zeitgebers, other than melatonin, has been scarcely investigated in humans, but data from animal studies clearly show that they play an important role in setting circadian clocks in peripheral oscillators of different organs (for a review see Dibner et al., 2010). Thus, although light–dark cycles serve as the major Zeitgeber for the central SCN clock, meal timing or feeding–fasting cycles are the dominant synchronization cues for peripheral oscillators. As a consequence, the central SCN clock that responds to light cues can get out of synchrony with peripheral organs that primarily respond to feeding time. In this case, we can speak of a mistimed internal synchronization (Figure 2).

1.3 | Non-visual effects of light

From a neuroanatomical perspective, it makes fully sense, that "light" is predisposed to be an important Zeitgeber in mammals. Light enters the eye and hits the retina, which is directly connected with the SCN via the retino-hypothalamic pathway (Figure 3). Thus, the SCN, optimally located above the optic chiasm in the anterior hypothalamus, receive constant information about the light–dark situation in the outside world. Interestingly, most of this non-visual light information is transmitted to the rest of the brain by a relatively newly discovered photoreceptor system; the so called intrinsically photosensitive retinal ganglion cells (ipRGCs; Berson, Dunn, & Takao, 2002; Hattar, Liao, Takao, Berson, & Yau, 2002). These cells also integrate light signals from visual photoreceptors, such as the rods and cones, to adapt the SCN clock to the external day–night cycle (Lucas, 2013). Accordingly, the eye is a dual sensory organ responsible for vision via the classical photoreceptors the rods and ones, but also crucial for circadian photoentrainment via the non-classical ipRGCs, which contain melanopsin as a photopigment (Provencio et al., 2000). The absorption spectrum of melanopsin is different from the short-wavelength, medium-wavelength and long-wavelength cones, as well as the rods, and peaks at ~480 nm in mammals (Lucas et al., 2014). Thus, the eye consists of five distinctive photoreceptors, which are differentially activated depending on the spectral composition of a given light source. As a matter of fact, light with a high spectral power ~480 nm predominantly drives circadian responses to light such as melatonin suppression (Brainard et al., 2001; Cajochen et al., 2005; Lockley, Brainard, & Czeisler, 2003; Thapan, Arendt, & Skene, 2001) or circadian phase shifts of the melatonin profile (Lockley et al., 2003). Natural light or sunlight has a rather high proportion of light in this spectral region and is thus ideal for circadian photoentrainment. On the other hand, the abundant use of artificial light in our 24/7 society, particularly in the evening and at night when the circadian timing system "needs" darkness and very sensitively responds to light (Figure 3), bears the risk of disturbing the daily adjustment between *inner* and *external* time. Too much light at night compromises the sharp demarcation between day and night, which existed during most of our ancestral development and is needed for proper circadian entrainment. Thus, in a modern society

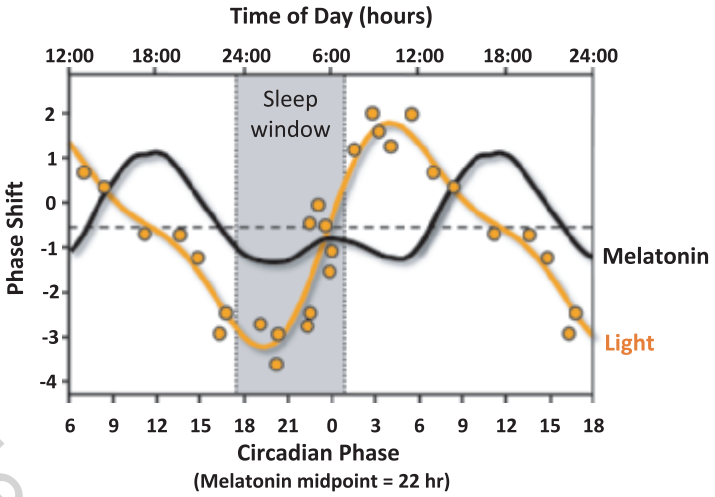

FIGURE 3 Human phase response curve (PRC) to the main Zeitgeber light and the non-photic Zeitgeber melatonin. The light was administered for 6.7 hr with an intensity of 10,000 lux for each study participants (individual yellow dots) at a different circadian phase/corresponding clock time (on the abscissa), whilst melatonin was administered as a pill of 0.5 mg. Phase shifts of the dim-light melatonin onset (DLMO, i.e., the timing of the onset of melatonin secretion under dim-light conditions) are plotted against the time of administration of the melatonin pill relative to the baseline DLMO (top x-axis). Phase advances (positive values) and delays (negative values) are plotted against the timing of the centre of the light exposure relative to the melatonin midpoint on the prestimulus constant routine protocol (defined to be 22 hr). The horizontal dashed line represents the anticipated 0.54 hr average delay drift of the pacemaker between the pre- and poststimulus phase assessments. The grey area limits the timing of usual bedtime. The light PRC data were redrawn from (Khalsa, Jewett, Cajochen, & Czeisler, 2003), whilst the melatonin PRC was redrawn from (Burgess et al., 2010)

the Zeitgeber strength of light may be impaired, particularly in shift workers exposed to irregular light–dark cycles. Shift work imposes a real challenge for the circadian clock for its proper entrainment to the outside world, as well as for an appropriate synchronization between the central and peripheral clocks (Figure 2).

Beyond circadian photoentrainment, light has a plethora of non-visual effects on human and animal behaviour, particularly direct effects on alertness, sleep, and mood (Cajochen, 2007; Hubbard, Ruppert, Gropp, & Bourgin, 2013). Recent experiments suggest that the circuit that connects ipRGCs to the SCN to align the body's circadian rhythm with light does not control the direct effect of light on wakefulness, mood, and learning (Fernandez et al., 2018; Rupp et al., 2019). Thus, the direct effects of light appear to utlilize distinct ipRGC output streams independently of the SCN's pacemaker function.

1.4 | Chronotypes

Circadian clocks differ between individuals in terms of their period length (i.e., *tau*) and amplitude as well as their phase of entrainment. The phase of entrainment describes at which circadian phase humans usually start their major sleep episode and their main episode of wakefulness. Typically, we roughly spend one-third asleep and two-thirds awake during a circadian cycle. The timing of both the sleep and wake episodes within the circadian cycle depends on chronotype. Thus, later chronotypes ("owls") usually do not only have a longer tau and a later circadian phase, but also an altered circadian phase of entrainment compared to morning types ("larks") (Duffy, Dijk, Hall, & Czeisler, 1999). Consequently, early chronotypes wake-up early in the morning and fall asleep early in the evening, and *vice versa* late chronotypes fall asleep late in the evening and wake-up late in the morning. Interestingly, mutations in core clock genes cause human circadian rhythm sleep disorders, particularly related to chronotype such as in advanced and delayed sleep phase syndrome (Blum, Bell, & Wu, 2018). Besides genetic traits, chronotype depends also on age, gender, and how an individual copes with the challenges of civil time and social time (e.g., work schedules etc.; Roenneberg, Pilz, Zerbini, & Winnebeck, 2019). Moreover, there is evidence that late and early types differ also in light sensitivity (Moderie, Van der Maren, & Dumont, 2017) and in sleep homeostasis (Schmidt et al., 2009; Taillard, Phillip, Coste, Sagaspe, & Bioulac, 2003). Despite considerable inter-individual and intercultural differences in the timing of sleep and wakefulness, to best of our knowledge clear night-active human ethnic groups or cultures do not exist.

The distribution of chronotypes within a given population is normal and ranges from extremely early to extremely late chronotypes (Roenneberg et al., 2019). In contrast to the normal distribution of chronotypes, school- and work-times are fairly narrowly distributed within the major part of the non-shift working population. Consequently, late chronotypes might be forced to get up before their biologically driven wake-up time, whereas early chronotypes might have to stay up longer into their biological night. For late chronotypes, the combination of early wake-up times (controlled by external timing) along with late sleep onset (controlled by internal time)

leads to the accumulation of sleep debt on workdays, which will then be compensated for on work-free days by sleeping longer. This discrepancy between internal and external timing is quantified by the absolute difference between mid-sleep on workdays and mid-sleep on work-free days and is referred to as "social jetlag" (Roenneberg et al., 2019). Although late chronotypes suffer more from social jetlag, early chronotypes do suffer from social jetlag as well, for example, when early chronotypes stay up long into the night without the possibility of sleeping longer the following day due to their normal wake-up time.

Both chronotype and social jetlag have been reported to be associated with different adverse health outcomes and unhealthy habits (Fabbian et al., 2016). Late chronotypes report lower sleep quality and more daytime sleepiness (Giannotti, Cortesi, Sebastiani, & Ottaviano, 2002; Taillard et al., 2003; Volk, Dyroff, Georgi, & Pflug, 1994), more depressive symptoms (Levandovski et al., 2011), and less healthy lifestyles and dietary habits (Kanerva et al., 2012; Malone et al., 2016). Furthermore, they have a higher risk for type 2 diabetes (Merikanto et al., 2013), and consume more alcohol, nicotine, and caffeine (Adan, 1994; Wittmann, Dinich, Merrow, & Roenneberg, 2006). Likewise, more social jetlag is associated with more depressive symptoms (Levandovski et al., 2011), increased body mass index and obesity (Parsons et al., 2015; T. Roenneberg, Allebrandt, Merrow, & Vetter, 2012), as well as increased consumption of nicotine, caffeine, and alcohol (Wittmann et al., 2006).

1.5 | Circadian drive for sleep and wakefulness

Circadian rhythms drive our lives most noticeably via the sleep–wake cycle. The latter includes sustained periods of quiescence occurring in a circadian pattern, reduced sensitivity to stimuli, and a homeostatic rebound following prolonged wakefulness. Although humankind has developed artificial light to allow being awake and working at night, we never fully adapt to a nocturnal behaviour with optimal cognitive performance at night and optimal sleep during the day. This is mainly due to the fact that the circadian timing system promotes sleep and wakefulness at specific time points within the 24-hr cycle thereby interacting with a sleep homeostatic process (for a review see Cajochen, Chellappa, & Schmidt, 2010). This has been conceptualized already in the 1980s with the two-process model of sleep regulation by Daan, Borbely and Beersma (Borbely, 1982; Daan, Beersma, & Borbély, 1984). In the meantime abundant physiological correlates for this model have emerged ranging from genetics, metabolomics and proteomics to neurophysiology (for a review see Borbely, Daan, Wirz-Justice, & Deboer, 2016).

The crucial role of circadian pacemaker neurones in sleep regulation is demonstrated by the loss of cycling of sleep–wake behaviour in flies and mice when these neurones are ablated (Eastman, Mistlberger, & Rechtschaffen, 1984; Renn, Park, Rosbash, Hall, & Taghert, 1999; Tobler, Borbély, & Groos, 1983). Furthermore, two case studies with patients with damage to the SCN region reported disrupted circadian pattern of body temperature and behaviour function (Cohen & Albers, 1991) and posttraumatic irregular sleep–wake rhythms (DelRosso, Hoque, James, Gonzalez-Toledo, & Chesson, 2014).

Findings acquired under a variety of experimental conditions looking at the circadian regulation of sleep clearly point to the existence of a powerful and active drive for wakefulness at the end of the habitual waking day in humans (Dijk & Czeisler, 1994, 1995; Lavie, 1986) (Figure 4). Thus, in humans the central SCN clock tunes peak arousal levels maximally in the evening hours around the onset of endogenous melatonin secretion (Figure 4). Accordingly, this time window has been named the circadian "wake-maintenance zone" by Strogatz, Beersma, Enright, and Gander (1987). At first glance the endogenous timing of the wake maintenance zone at the end of the habitual waking day seems paradoxical (Dijk & Czeisler, 1994). However, in combination with the continuous increase in homeostatic sleep pressure throughout the habitual waking day, it makes perfect sense such that the circadian wake drive is opposing maximal sleep pressure levels in the evening. This prevents us from falling asleep early in the evening hours thereby ensuring a consolidated period of wakefulness. Shortly thereafter the circadian wake promotion stops abruptly, and the nocturnal onset in melatonin secretion initiates a cascade of events that culminates ~1.5–2 hr later in the opening of the "sleep gate" (Shochat, Haimov, & Lavie, 1998; Figure 4). Interestingly, SCN-lesioned squirrel monkeys reduced the length of their wake bouts by a factor 15 during the subjective day but not during the subjective night, leading the investigators to suggest that the circadian clock is actively involved in the promotion of wakefulness, by opposing the homeostatic accumulated drive for sleep (Edgar, Dement, & Fuller, 1993). It was also proposed that the circadian pacemaker may actively promote sleep in the early morning hours, when homeostatic sleep pressure has mostly dissipated (Dijk & Czeisler, 1994, 1995; Lavie, 1986). With age, the strength of circadian wake promotion in the evening weakens (Münch et al., 2005), which could explain why some older people have difficulties in staying awake during evening hours, whilst the opposite is true for teenagers and young adults (Frey, Balu, Greusing, Rothen, & Cajochen, 2009). A strong evening circadian wake promotion can also mask accumulated sleep pressure across working days and preventing many people from going to bed earlier to compensate for sleep loss. Early evening administration of melatonin acts as a "*Chrono-quiescent*" reducing circadian wake promotion and thereby allowing for an earlier bedtime.

Thus, in humans, endogenous melatonin release from the pineal gland, which is under direct control of the SCN may help in the transition from wakefulness to sleep as a physiological "night signal." Concurrent with the onset of melatonin secretion, core body temperature is downregulated via vasodilation in the extremities, which is *per se* a strong thermoregulatory signal for relaxation needed for a smooth transition from wakefulness into sleep in humans (Kräuchi, Cajochen, Werth, & Wirz-Justice, 1999).

How circadian oscillations in the SCN interact with circuits controlling for states of sleep and wakefulness at the cerebral level is still an open question. Output of the SCN indirectly reaches

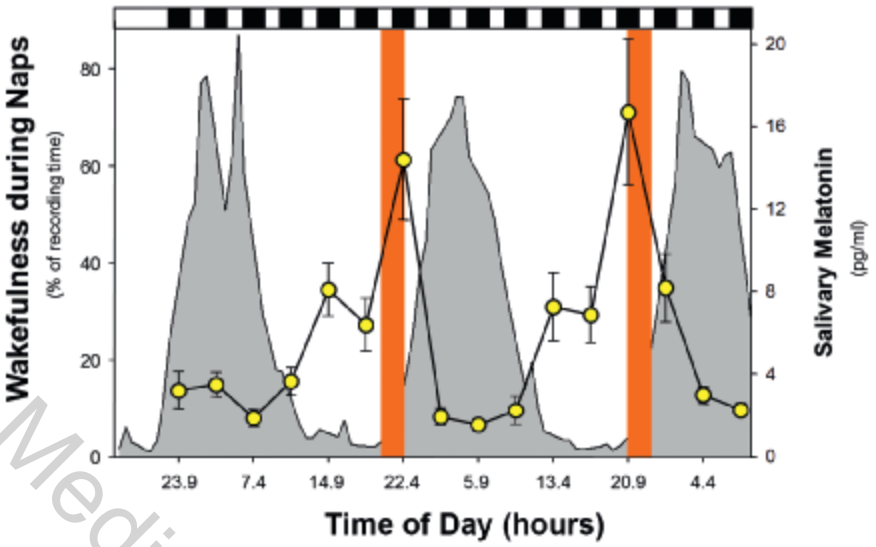

FIGURE 4 Temporal association between the sleep ability during a multiple nap protocol across 64 hr in a constant semi-recumbent body position under dim light (<8 lux) conditions and endogenous circadian melatonin secretion (in grey). The timing of the scheduled naps (75 min) and scheduled wakefulness (150 min) is indicated in black bars and white bars respectively on the above abscissa. Time of day is the unit of the *x*-axis. Sleep ability is indexed by the amount of wakefulness (% of total nap time, yellow dots) during a given nap. The wake-maintenance zone on the first and second evening is delineated with boxes in orange and clearly occurs around the onset of melatonin secretion in the late evening followed by the "opening of the sleep gate." Data represent average values of 12 healthy study volunteers (unpublished data from the Centre for Chronobiology, University of Basel, Switzerland)

target areas implicated in the regulation of sleep and wakefulness such as the ventro-lateral-preoptic area (VLPO), tuberomammillary nucleus lateral hypothalamus the zona incerta, thalamus, and brainstem nuclei via its connections to the dorsal medial hypothalamus (DMH) (Cedernaes, Waldeck, & Bass, 2019; Mistlberger, 2005). Concomitantly, diffuse monoaminergic activating systems are under circadian control and impinge on many thalamocortical areas, suggesting that the interaction with sleep homeostasis could take place at many different levels (Dijk & Archer, 2009). Work by Aston-Jones (2005) and by Aston-Jones, Chen, Zhu, and Oshinsky (2001) has shown that the noradrenergic locus coeruleus (LC) system plays an important role in the circadian regulation of alertness. Within the framework of their model, the SCN indirectly communicates with the LC via projections to the DMH. Evidence for that comes from neurophysiological experiments, which revealed circadian variations in LC impulse activity and showed that lesions of the DMH eliminated these circadian changes in LC activity, suggesting a functional significance of the SCN–LC circuit (Gompf & Aston-Jones, 2008). Through LC activity, with its widespread thalamic and cortical connections, this pathway may control a variety of central nervous system functions related to noradrenergic innervations, including alertness and vigilance, and also higher order cognitive processes. The SCN also projects to the lateral hypothalamic area (LHA; Horvath et al., 2012), which contains wake-promoting hypocretin-expressing neurones that are critical for proper regulation of sleep–wake state and transitions across sleep stages (Adamantidis, Zhang, Aravanis, Deisseroth, & de Lecea, 2007; Sakurai et al., 1998). Besides wake-promoting neurones, also sleep-active neurones that express melanin-concentrating hormone and gamma-aminobutyric acid (GABA)ergic neurones were found in the LHA. As such, the LHA demonstrates how intermingled cells within the same region can have opposing physiological functions (for a review see Cedernaes et al., 2019). Similarly, the VLPO, a sleep-active brain region that releases the inhibitory neurotransmitters galanin and GABA, may change its functionality (for a review see Deboer, 2020). Optogenetic stimulation shows that low-frequency stimulation (1–4 Hz) of the VLPO indeed promotes sleep, but frequencies >8 Hz induce waking (Kroeger et al., 2018).

Studies investigating human brain responses to sustained attention under differential sleep pressure conditions across time of day via functional magnetic resonance imaging yielded activity in subcortical regions, which mainly followed the endogenous circadian clock (Muto et al., 2016) and attention-related cerebral activity in anterior hypothalamic structures, putatively implicated in the regulation of the circadian wake-promoting signal (Schmidt et al., 2009). In contrast to subcortical areas, which are affected by circadian rhythmicity, the human cortex seems to be influenced by the interaction between sleep homeostasis and the circadian-timing system, with frontal areas showing strong sleep homeostatic influences progressively decreasing towards posterior areas, which exhibit stronger circadian modulations than frontal areas (Cajochen, Wyatt, Czeisler, & Dijk, 2002).

To sum up, the SCN exerts a profound influence on sleep–wake timing via a multiple interplay between circadian and homeostatic oscillators. In humans, active circadian wake promotion during the subjective evening facilitates stable alertness levels throughout a normal

waking day, by opposing the increasing homeostatic sleep pressure at this time of the day. Likewise, circadian sleep promotion occurs in the early subjective morning hours after homeostatic sleep pressure has dissipated allowing for a consolidated bout of night sleep.

1.6 | Circadian (sleep) medicine

Temporal organization of biological processes is essential for human health (Bedrosian & Nelson, 2017). Disorders of endogenous circadian rhythms have traditionally been considered to impact primarily on sleep timing and therefore to pertain to the field of sleep medicine. The International Classification of Sleep Disorders, third edition (ICSD-3) distinguishes between seven different circadian rhythm sleep–wake disorders, which result from a misalignment between the 24-hr light–dark cycle or the socially acceptable time for sleep and wakefulness and the internal biological clock, due to intrinsic (i.e., delayed and advanced sleep-wake phase disorder, non-24-hr and irregular sleep–wake rhythm disorder) or extrinsic causal factors (i.e., shift work and jet lag disorder; Darien, 2014; American Academy of Sleep Medicine, 2014).

However, recent advances in circadian research indicate that molecular circadian clocks are present in nearly all the body's tissues and cells (Panda, 2016). The evidence that circadian genes not only coordinate biological timing, but also modulate several physiological functions, including metabolism, inflammation, and cellular repair processes, has led to a better understanding of the central role of circadian disruption in chronic diseases, for example, hypertension, diabetes, and cancer, which highlights the importance of chronobiology for medicine (Zee, 2019).

In general, alteration of a proper circadian organization (circadian health) is involved in the pathophysiological models of a variety of conditions beyond the traditional sleep–wake rhythm disorders. Therefore, the new field of circadian medicine is rapidly evolving, focussing on clinical interventions that target the circadian timing system in order to improve overall health (Abbott, Malkani, & Zee, 2020). Some examples are represented by conditions such as shift work, metabolic, neurodegenerative and mood disorders. Moreover, circadian medicine encompasses the field of chronopharmacology, which aims at optimizing the timing of drug administration in order to maximize their efficacy and reduce their adverse effects (Ruben, Smith, FitzGerald, & Hogenesch, 2019).

1.6.1 | Shift work

From the large-scale diffusion of electric light in the last century, to the development of a 24/7 society, which requires longer and non-conventional working hours, overnight shift work has been increasingly demanded, making it more difficult to synchronize sleep–wake behaviour and biological timing. Night-shift workers are very often exposed to artificial light whilst awake when the circadian clock anticipates darkness and promotes sleep. On the other side, they are supposed to sleep during the day at an adverse circadian phase, when the circadian pacemaker promotes wakefulness and the endogenous melatonin levels are low. As a result, they experience sleep problems, fatigue, poor memory and performance, gastrointestinal disturbances, and have a greater risk of work-related accidents and injuries (Foster & Kreitzman, 2017). Moreover, shift work has been associated with an increased long-term risk of cardiovascular diseases, diabetes, and some types of cancer (Kecklund & Axelsson, 2016). As an example, night-shift workers have a higher risk of developing type 2 diabetes, which depends on the number of night shifts per month (Vetter et al., 2018). Also, in June 2019 the International Agency for the Research on Cancer concluded that night-shift work is probably carcinogenic to humans (Group 2A) (Ward et al., 2019), thus drawing attention to the public health consequences of living and working against the endogenous clock and pointing to the occupational risk factors of shift work, in order to improve the work environment (Erren, Morfeld, Gross, Wild, & Lewis, 2019).

1.6.2 | Metabolic disorders

Both animal and human models suggest that sleep disruption and circadian misalignment contribute to cardiovascular, inflammatory and liver diseases, as well as to obesity and metabolic disorders (Abbott et al., 2020). Healthy volunteers undergoing chronic sleep deprivation in constant routine laboratory protocol showed a lower glucose tolerance and reduced insulin sensitivity (Sinturel, Petrenko, & Dibner, 2020). Similar adverse metabolic outcomes were found in individuals subjected to an experimentally forced circadian misalignment (Sinturel et al., 2020). On the other hand, time-restricted eating improved blood glucose control and reduced blood pressure in men at risk of prediabetes, without causing weight loss (Panda, 2019). Overall, it has become increasingly clear that not only the composition of diet, but also the temporal coordination between timing of meals and internal metabolic clocks is important for metabolic health, affecting weight loss and plasma lipid profiles (Sinturel et al., 2020). Thus, resynchronization of the sleep–wake cycle with the eating/feeding rhythm represents a promising approach in preventing and treating metabolic disorders. Circadian interventions such as time-restricted eating based on the individual chronotype along with scheduled exercise, or morning light therapy, have been shown to improve metabolic health by increasing circadian amplitude and sustaining robust circadian rhythms (Allen et al., 1992; Chaix, Manoogian, Melkani, & Panda, 2019). Taken together, these strategies may help to effectively counteract the increasing incidence of metabolic diseases in our society.

1.6.3 | Neurodegenerative disorders

Circadian disruption seems to have a bidirectional relationship with neurodegeneration, being a consequence of neurodegeneration,

but possibly also a causative factor contributing to the neurodegenerative cascade (Videnovic, Lazar, Barker, & Overeem, 2014). In Alzheimer's disease (AD) and related dementias, or Parkinson's disease (PD), an alteration of sleep–wake cycles, hormone secretion, and body temperature, as well as a dysregulation of the autonomic system are common (Abbott et al., 2020). Patients with AD tend to have high fragmentation and slightly reduced amplitude of circadian rhythms, whilst patients with PD also show reduced circadian amplitude, but no changes in circadian phases (Leng, Musiek, Hu, Cappuccio, & Yaffe, 2019). The severity of circadian rhythm disruption depends on the stage of neurodegeneration, as well as the received treatment (Leng et al., 2019). Interestingly, several studies suggest that an altered circadian function may be present at the preclinical stage of AD and other dementias, and therefore be considered an early marker or prodrome for neurodegenerative diseases (Tranah et al., 2011). Future research will shed more light on a possible role of circadian misalignment in causing neurodegeneration and on the efficacy of personalized circadian interventions in preventing or delaying the onset of neurodegenerative processes amongst healthy older adults. Circadian disruption might therefore represent a promising therapeutic target in the prevention and management of neurodegenerative disorders.

1.6.4 | Mood disorders

Sleep and circadian rhythm disruption might not only represent a risk factor for psychiatric disorders, but also contribute to disease progression and even be a target for treatment (Wulff, Gatti, Wettstein, & Foster, 2010). However, the mechanisms underlying this association remain poorly understood. Several clock genes polymorphisms have been found in patients with both abnormal sleep timing and affective disorders (Garbazza & Benedetti, 2018). Moreover, as mood is partly under circadian and homeostatic control, mood instability may also depend on an abnormal phase relationship between these two processes, which also regulate sleep and wakefulness. Sleep deprivation, light therapy, and an imposed sleep schedule at night may have rapid antidepressant effects by optimizing the interplay between circadian and homeostatic processes (Benedetti, Barbini, Colombo, & Smeraldi, 2007; Wirz-Justice & Van den Hoofdakker, 1999), thus confirming the pathophysiological hypothesis linking sleep and circadian factors to affective disorders (Bunney & Potkin, 2008).

1.6.5 | Chronopharmacology

Chronopharmacology is a highly promising approach in disease management based on the concept that the efficacy of medications can be potentiated, and their toxicity reduced, by timing their delivery (Ruben et al., 2019) (Sinturel et al., 2020). As pharmacological treatments often target molecular components that exhibit rhythmic oscillations, knowledge of circadian rhythms can be utilized in future personalized and precision medicine.

2 | CONCLUSIONS

Circadian rhythms affect nearly all aspects of physiology, and are involved in the regulation of several biological processes beyond the timing of sleep and wakefulness. Therefore, circadian health is rapidly establishing as a key factor for the success of preventive and treatment strategies. This opens a new field of research with significant clinical implications, represented by circadian medicine.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

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