Running title: “Light in ecological settings”

Title: “Light in ecological settings: entrainment, circadian disruption, and interventions”

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Abstract

Light is the predominant signal for the human circadian clock to synchronize to the solar 24-h day through an active process called entrainment. Modern light profiles are characterized by exposure to both natural daylight and artificial lighting. A mismatch between these self-selected light profiles and the solar day-night alternation can disrupt the circadian system, resulting in acute and chronic effects for health and safety. In this chapter, we describe (i) how entrainment works in the real world, illustrating the major role of light for this process; (ii) ways in which the circadian system can be disrupted by (external) factors such as irregular sleep, shift work, daylight saving time, and longitudinal position in a time zone; and (iii) how field studies have used light interventions to reduce direct and indirect effects of circadian disruption in ecological settings.

Keywords

Circadian, Sleep, Sleep regularity, Chronodisruption, Shift work, Social jetlag, Entrainment, Chronotype, Occupational

1 Introduction

After fast travels across time zones, sleepiness, digestion problems, and cognitive impairment are common symptoms of 'jet lag malaise', a syndrome that occurs when the body is not in synchrony with the new local time at destination (Sack, 2009). Twice a year, people in several countries experience a 'mini jet lag' caused by transition into and out of daylight saving time that pushes seasonal solar progression back by several weeks (Kantermann et al., 2007). Increasingly more workers engage in permanent or rotational shift work experiencing acute and chronic health effects by sleeping, eating and being active when biological functions require the opposite (Drake and Wright, 2011). What all three phenomena have in common is the disruption of internal, biological rhythms, most obviously that of the daily sleep-wake cycle. Life, and therefore biology, is embedded into a temporal structure of light and dark, of warm and cold, created by the earth's 24-h rotation. Anticipating cyclic environmental changes, both, within a day and over the year, permits organisms to occupy not only spatial and social niches in ecology, but also temporal ones. In millions of years of evolution, all living organisms have evolved a mechanism enabling them to measure time and predict periodic changes – the circadian clock, governing behavior and physiology in bacteria, plants and animals, including humans. The word *circadian* (lat. 'circa' – about, 'dies' – a day) reflects that the periodicity of the internal clock is 'approximately one day' rather than precisely 24h (Halberg, 1959). When shielded from environmental time cues and kept in constant conditions, the circadian clock 'free-runs' generating an endogenous day that is slightly longer than 24h, averaging 24h 11min ± 8 min in humans (Czeisler et al., 1999). 'Free-running' refers to the ability of the clock to exhibit a self-sustained rhythm, i.e., to continue oscillating with an intrinsic period *tau* (τ) in the absence of external cues. In humans, the master clock resides in the brain in a pair of nuclei of ~20,000 neurons above the crossing of the optic nerves, the suprachiasmatic nucleus (SCN). The SCN exhibits a self-sustained rhythm in neuronal firing rate with a circadian period τ. In order to adjust its endogenous circadian cycle

length to precisely the 24h period of the external solar day, the SCN receives light input from the retina via a direct axonal pathway, the retino-hypothalamic tract. Unlike other vertebrates, photoreceptors in mammals are exclusively ocular (Freedman et al., 1999; Wright and Czeisler, 2002). In humans, light expresses its non-visual, circadian effect through 'intrinsically photosensitive retinal ganglion cells' (ipRGCs), which make up ~1% of all retinal ganglion cells (Berson et al., 2002; Provencio et al., 2000). These ipRGCs express the photopigment melanopsin, with a spectral sensitivity that peaks in the short wavelength range, identifying blue light as the most relevant spectrum color for the circadian system (Brainard et al., 2001; Revell et al., 2005; Wright et al., 2004).

It took centuries of research to prove that behavioral and physiological rhythms were endogenously generated rather than the result of a mere response to external periodic changes. Today, a free-running rhythm with a cycle length deviant from 24h in constant conditions is considered one of three major characteristic of circadian clocks ('self-sustainability'), together with 'temperature compensation' (a functional clock must compensate for temperature differences that otherwise would accelerate or decelerate chemical processes and consequently alter the clock's period) and 'entrainability', which describes the intricate process through which the circadian system actively synchronizes its non-24h period with the exact 24h-period of the solar day. In this chapter, we will (i) briefly introduce models of entrainment including the dominant role of light for this process (Section 2), (ii) address what happens when the entrainment process is complicated by external factors such as shift work disrupting the circadian system (Section 3), and (iii) present ways in which light has been used in the field to prevent or mitigate adverse consequences of circadian disruption (Section 4).

2 Entrainment in humans: Light as the dominant *zeitgeber*

In order for the organism to accurately predict and thus be prepared for periodic environmental changes, the circadian system needs to be in synchrony with the external light-dark cycle as the alternation of light and darkness provides the most precise and reliable signal in the environment for time of day. Besides self-sustainability and temperature compensation, 'entrainability' is a major feature (if not 'the' feature) of circadian clocks. Entrainment describes the synchronization process of the circadian clock to daily environmental changes, *e.g.,* the light-dark alternation created by the earth's 24-h rotation. By simply responding to external changes, any time-responsive system could be passively synchronized. In contrast, entrainment is an active process during which the circadian system as a self-sustaining oscillator assumes a specific phase relationship with an external rhythm that is able to reset the clock (Roenneberg et al., 2003). Any periodic signal that can reset and shift the clock is called 'zeitgeber' (from the German word for 'time giver'). The phase angle between two rhythms is called *phase of entrainment* Ψ and relates the reference point of an internal circadian rhythm with that of the external zeitgeber cycle (*e.g.,* timing of core body temperature minimum relative to sunrise). The minute-deviations of free-running rhythms from 24h have led to the argument that entrainment of the clock is needed to correct for that deviation. Yet, organisms do not encounter constant conditions producing free-running rhythms in real life, as the rotation of the earth and its non-perpendicular North-South axis cause daily and seasonal variability in, e.g., photoperiod. Thus, the mechanisms behind a functional clock have evolved in a reliably changing environment. Accordingly, the circadian clock does not entrain because its free-running rhythm is not exactly 24h but it free-runs with a non-24h period to ensure optimal functioning *when entrained* (Roenneberg et al., 2003; Roenneberg and Merrow, 2002). The phase of entrainment is not fixed but depends on several parameters: the endogenous period τ, the external zeitgeber period T, its light:dark ratio (photoperiod), as well as amplitude (strength) of the zeitgeber rhythm. Light turned out to be the predominant zeitgeber for the central circadian clock across the animal and plant kingdom, including humans. In the

following section, we present three major approaches that have been proposed to predict how circadian clocks entrain to light-dark cycles.

2.1 Models of Entrainment

All three approaches are so-called ‘phase-only models’ as their only read-out is circadian phase. They all agree that stable entrainment is reached when the difference between internal and external period is somehow corrected for but postulate different response characteristics to achieve this ‘correction’.

2.1.1 Non-parametric entrainment (PRCs)

Colin Pittendrigh, one of the circadian field’s pioneers, approached entrainment by systematically investigating responses to transient light pulses while keeping animals in constant darkness (Pittendrigh et al., 1958). From his experiments, he concluded that the system is instantaneously shifted to a new phase when perturbated by a light stimulus. Stable entrainment is thus reached when the discrete phase shift ($\Delta\varphi$) corrects for the deviation of the endogenous cycle length (τ) from 24h (T), that is $\Delta\varphi = \tau - T = 0$. The circadian system’s response will depend on when the stimulus is presented, summarized in *phase response curves* (PRCs) plotting the magnitude of a phase shift as a function of circadian phase. PRCs for brief light pulses are characterized by a phase delaying and a phase advancing region, usually separated by a ‘dead zone’ where no or insignificant phase shifts are seen (Figure 1). This approach was termed non-parametric entrainment as it assumes discrete instantaneous phase resetting in response to transient light pulses leaving the oscillator itself unaltered. A PRC for light was also demonstrated in humans, with the delay region showing a larger amplitude than the advance region (maximum phase shift: -3.3h delay vs. 1.8h advance) (Khalsa et al., 2003).

----------Insert Figure 1 here----------

2.1.2 Parametric entrainment (VRCs)

A parametric approach to entrainment was proposed by Jürgen Aschoff, another pioneer of the circadian field, to account for effects of continuous light exposure rather than single light pulses (Aschoff, 1964). He postulated that stable entrainment was achieved by changing the clock's velocity, and consequently its phase, in order to match internal and external cycle length. *Velocity response curves* (VRCs) are estimated from PRCs, based on responses to light compared with constant darkness. Essentially, parametric and non-parametric entrainment differs mainly by the nature of the light stimulus (*i.e.,* transient vs. continuous) (Roenneberg et al., 2010). A fundamental problem that PRCs and VRCs face is the assumption of a stable τ and P(V)RC itself. This view is challenged by the observation that τ changes dependent on zeitgeber conditions (*i.e.* after-effects of entrainment (Daan and Pittendrigh, 1976; Scheer et al., 2007), intensity of constant light (Aschoff, 1979)). Thus, a third approach has been proposed postulating that model predictions should not be derived from artificial conditions such as brief light pulses or constant darkness but from naturalistic conditions, i.e., when circadian rhythms are synchronized.

2.1.3 Integrated entrainment (CIRCs)

Roenneberg et al. (2010) have suggested a model of entrainment that is accessible from data under entrained conditions. Their concept does not assume mechanisms by which internal and external cycle lengths are matched (*i.e.* phase shifts, velocity changes) but integrates effects of light at different internal times as formalized by a *circadian integrated response characteristic* (CIRC). The CIRC assumes that light around subjective dawn compresses the internal cycle (resulting in phase advance), light around subjective dusk expands it (leading to phase delay), and a 'dead zone' separates both these parts. Its form is determined by two factors: the asymmetry of the compressing and expanding regions and the extent of the dead zone (making the CIRC more or less sinusoidal). Light exposures of any form (from single light pulses to

extended and multiple light signals) are integrated over one cycle, and stable entrainment is reached when τ = T, *i.e.* the internal period adjusts to the external cycle length via compression or expansion.

2.1.4 Phase of entrainment

A successful entrainment process results in a stable phase of entrainment. However, as pointed out above, the phase of entrainment is not fixed but depends on several factors, including circadian period τ, zeitgeber strength (amplitude of T), and photoperiod (light:dark ratio). All three entrainment approaches predict that shorter circadian periods (<24h) result in earlier circadian phases and longer periods (>24h) in later phases. The CIRC makes additional predictions regarding the effect of zeitgeber strength on phase of entrainment. Zeitgeber strength refers to the amplitude of the zeitgeber rhythm. For instance, the amplitude of the light-dark cycle increases when the difference between day and night becomes more pronounced (e.g., with more sunlight exposure in summer) and decreases when the line between day and night is blurred (e.g., due to increased exposure to electrical light in the evening). The CIRC predicts that with increasing amplitude of the zeitgeber cycle, the distribution of phases of entrainment within a population will become narrower, which has been confirmed by studies in humans (Beale et al., 2017; Moreno et al., 2015; Pilz et al., 2018; Wright et al., 2013) and birds (Dominoni et al., 2013). Consequently, under strong and weak zeitgeber conditions, two individuals with identical τ will assume different phases of entrainment whereas two individuals with different τ can assume the same phase. Individuals thus entrain differently, depending on their endogenous circadian make-up (e.g., τ) and their (self-selected) light exposure. The resulting circadian phenotypes have been coined ‘chronotypes’, describing differences between individuals in their relative timing of behavior (e.g., sleep, activity, food intake), cognition (e.g., alertness), and physiology (e.g., hormone release, body temperature) (Baehr et al., 2000; Duffy et al., 2001; Kerkhof, 1985; Tankova et al., 1994).

2.2 Chronotypes

The term chronotype was originally proposed in 1974, referring to “an organism’s temporal organization” (Ehret, 1974). Defining chronotype as phase of entrainment Ψ in a circadian framework, it is viewed as a biological construct rather than a psychological trait (Roenneberg, 2015; Roenneberg et al., 2019a). The master pacemaker in the brain, the SCN, orchestrates a peripheral, multi-oscillatory system throughout the body, where different oscillators assume different phase relationships with each other and the external zeitgeber (Menaker et al., 1997; Mohawk et al., 2012). As such, there is no single phase of entrainment that represents the state of the entire organism. However, the timing of individual clock-regulated processes (i.e., biomarkers) can be used to estimate chronotype, reflecting Ψ of that particular rhythm. In humans, such biomarkers include, e.g., dim-light melatonin onset (DLMO; Pandi-Perumal et al., 2007) and the peak time of activity (acrophase; Lim et al., 2012). Typically, however, chronotype is assessed based on behavioral rhythms, such as sleep-wake behavior, using questionnaires, sleep diaries, and/or activity-recording devices (actimetry/actigraphy). It is important to state that sleep timing is under the control of both circadian and homeostatic processes, as well as social and work constraints on when sleep can occur. As such, chronotype based on sleep-wake behavior is not a “pure” circadian output but nevertheless reflective of circadian rhythms, e.g., correlating with dim-light melatonin onset, a gold standard circadian marker ($r = 0.5$-0.7; Burgess et al., 2003; Kantermann et al., 2015; Kitamura et al., 2014). A comprehensive overview of the concept (including a trait vs. state discussion) and measurement of human chronotypes is provided by Roenneberg et al. (2019).

Human chronotypes (based on sleep-wake behavior) follow a distinct age- and sex-pattern (Figure 2): both men and women become later throughout adolescence, reaching a peak in ‘lateness’ at around 20 years of age, and become earlier again with increasing age. On average, men tend to be later chronotypes than women; this difference is reported to either disappear

(Roenneberg et al., 2004; Tonetti et al., 2008) or be reversed (Duarte et al., 2014; Fischer et al., 2017b) at the age of 40-50y. More than 50% of the lifelong chronotype change occurs during adolescence and early adulthood, while variability decreases with age (Fischer et al., 2017b). Chronotypes show a wide distribution, with differences of up to 10h between extremely early ("larks) and extremely late ("owls) types (Fischer et al., 2017b; Roenneberg et al., 2007). The observed wide distribution is likely due to a reduced zeitgeber signal, weakened by a combination of low indoor light intensities during the daytime and increased exposure to electrical light in the evening. Even low evening light intensities (<30 lux) have been shown to substantially delay sleep onset and suppress melatonin (a sleep-facilitating, clock-regulated hormone) (Chang et al., 2015; Phillips et al., 2019), whereas bright light exposure during the day has been shown to reduce melatonin suppression at night (Hébert et al., 2002; Smith et al., 2004).

----------Insert Figure 2 here----------

Individuals' exposure to light and darkness, whether externally imposed (e.g., seasonality, daylight saving time, shift/night work) or self-selected (e.g., via exposure to light-emitting devices in the evening), is a major determining factor for phase of entrainment/chronotype. Light is therefore a powerful intervention tool to increase or reduce chronotype differences, to align or mistime circadian phases, and consequently, to aggravate or alleviate consequences of circadian disruption. In the following sections, we will address how circadian disruption can arise from a misalignment of physiological and/or behavioral rhythms with the solar light-dark cycle (Section 3) and present ways that field studies have used light in ecological settings to alleviate circadian disruption and/or associated adverse consequences (Section 4).

3 Circadian disruption: how misaligned light-dark cycles can disrupt the circadian system

The term “circadian disruption” (along with “circadian desynchrony”, “circadian misalignment”, and “chronodisruption”) has been broadly used to refer to a mismatch between two or more circadian rhythms. More specifically, circadian disruption (CD) can be caused by internal or external factors and occur at several levels: systemic, organismal, and cellular (Qian and Scheer, 2016). External CD occurs at the systemic level and differentiates between environmental and behavioral misalignment. While both cases describe a misalignment with the endogenous SCN rhythm, the former refers to a misalignment between the SCN and an environmental, zeitgeber rhythm (i.e., the light-dark cycle), whereas the latter refers to a misalignment between the SCN and a behavioral rhythm, such as sleep-wake or feeding-fasting cycles. Internal CD occurs at the organismal (and cellular) level and describes a misalignment among endogenous rhythms, e.g., between the central pacemaker SCN (entrained by light) and peripheral clocks, such as in the liver (entrainable by feeding-fasting cycles, e.g., Wehrens et al., 2017). The misalignment of rhythms can be due to differences in phase and/or period. Historically, the terms desynchrony and desynchronization have been used to refer to differences in period (e.g., Aschoff, 1965), whereas circadian misalignment is used to describe an abnormal phase angle between two (or more) rhythms. Excellent overviews of concepts, definitions, and measurements of CD are provided by Vetter (2018) and Roenneberg & Merrow (2016).

Numerous studies have linked CD with adverse outcomes for health and safety, including endocrine, metabolic, and cardiovascular diseases (Bedrosian et al., 2016; Maury, 2019; Portaluppi et al., 2012; Stenvers et al., 2019), cancer (Battaglin et al., 2021; Patel and Kondratov, 2021; Shafi and Knudsen, 2019), psychiatric illnesses (Jones and Benca, 2015), neurodegenerative diseases (Carter et al., 2021; Musiek and Holtzman, 2016), accidents/injuries

(Williamson et al., 2011), and impaired cognitive performance (Goel et al., 2013; Taillard et al., 2021). In view of these studies, CD terminology is often used in a way that suggests changes in the circadian system are generally negative. As pointed out by Vetter (Vetter, 2018), it is critical to note, however, that the circadian system is inherently adaptive. Changes in circadian rhythms can be necessary to achieve a stable phase of entrainment, e.g., after travel. Such progressive phase transitions would not necessarily qualify as a detrimental disruption but as reflective of a functional circadian system. Another important aspect is the notion of CD as a modifiable risk factor: the magnitude of CD depends on both the challenge (or exposure, i.e., shift work) and the individual's circadian response characteristics (i.e., τ, Ψ). Given the same exposure (i.e., working the same shift schedule), individuals can experience different levels of CD based on their chronotype, e.g., early types experience higher levels of CD on night shifts than late chronotypes (Juda et al., 2013; Kervezee et al., 2021; Vetter et al., 2015). Likewise, the same individual can experience different levels of CD when exposed to different challenges (i.e., traveling across 2 vs. 6 time zones). Most studies have used the latter distinction to operationalize CD in field studies, using exposures such as shift work as (binary) proxies for CD. Other examples of exposures to operationalize CD in field studies include the position within a time zone and transitions into and out of daylight saving time (DST). We will briefly discuss these exposures in the following sections. What they all have in common is the shifting of sleep/work/clock times in relation to sun time, that is the local light-dark cycle (Figure 3). The result is a rhythm instability or irregularity, of which irregular sleep has recently gained attention as a proxy for CD in the field (Bei et al., 2016; Fischer et al., 2021).

----------Insert Figure 3 here----------

3.1 Sleep regularity

Until recently, epidemiological and laboratory studies of adverse effects of sleep on health and safety have focused on average sleep duration or timing. Emerging evidence, however, suggests that maintaining regular sleep-wake patterns (consistent sleep timing between days) may be more important to these outcomes than sleep duration (Bei et al., 2016; Lunsford-Avery et al., 2018; Pye et al., 2021; Watson et al., 2020). This represents a major shift in our understanding of what healthy sleep is: regular timing, not just adequate duration, is critical for health, cognitive performance, and general wellbeing. Sleep regularity associates with a wide range of outcomes, often in cases where other dimensions of sleep behavior, such as sleep duration, do not. For instance, in a cohort study of ~2,000 participants, sleep regularity was associated with metabolic syndrome, diabetes, obesity, hypertension, and elevated fasting blood glucose, whereas sleep duration was only associated with hypertension (Lunsford-Avery et al., 2018). This is possibly because irregular sleep may be a proxy for variability in other rhythms, such as light, meals, and exercise, and therefore reflects certain aspects of circadian disruption that average sleep duration and timing do not capture. Accordingly, associations between irregular sleep and health and performance outcomes could be mediated not by sleep itself, but by irregularity in other co-occurring factors, including light exposure. When sleep-wake patterns are irregular, light often extends into the night resulting in circadian disruption, given that the SCN is highly responsive to light (Phillips et al., 2019). Hence, light has the potential to disrupt the circadian system independent of sleep. For instance, exposure to room light for one night induced metabolic dysfunction in young healthy adults, whereas a night of sleep deprivation with dim light did not (Gil-Lozano et al., 2016). Up to date, it is unclear whether associations between irregular sleep and health might be mediated by irregularity in other co-occurring factors with the potential to synchronize the circadian system (i.e., light, meal timing, exercise).

3.1.1 Social jetlag

While highly irregular sleep-wake rhythms frequently occur in response to irregular work schedules, such as night work and rotational shift work, they also affect the wider population, with 80% experiencing at least some degree of irregular sleep by shifting sleep times between weekdays and weekends (Roenneberg et al., 2012). This phenomenon has been coined “social jetlag” by Roenneberg and colleagues (Roenneberg et al., 2012, 2019a; Wittmann et al., 2006) to describe a discrepancy between the biological, circadian clock and the social clock (i.e., work/school times, social/familial events). Social jetlag is a modern phenomenon that for most people is characterized by earlier and shorter sleep on weekdays and later and longer catch-up sleep on weekends. This irregular but systematic sleep-wake pattern is due to rise times for school and work that are too early for the circadian clocks of most people, which have been delayed by the widespread use of electrical lighting. The availability of artificial light allows individuals to create their own light-dark cycles, typically increasing their exposure to light in the evening, when it is already dark outside (Goulet et al., 2007; Phillips et al., 2019). This exposure to evening light weakens the zeitgeber strength (i.e., blurring the difference between day and night), delays the circadian clock and widens the chronotype distribution, with more later chronotypes than under stronger zeitgeber conditions (Chang et al., 2015; Roenneberg et al., 2010; Wright et al., 2013). The net result is a repeated shifting of sleep times between workdays and days off, that resembles sleep-wake patterns observed for travel crossing time zones but without the simultaneous change of the external light-dark cycle. While the change in the solar light-dark cycle drives re-entrainment and eventually resolves travel jetlag, this change is absent for social jetlag, where the solar light-dark cycle remains the same. Thus, social jetlag likely represents a chronic misalignment between rapidly shifting, self-selected light-dark exposure and an unchanged solar day-night cycle (leaving aside much slower seasonal changes) (Roenneberg et al., 2019a). Social jetlag is most pronounced in late chronotypes, and has been associated with a wide range of adverse outcomes, including increased risks of obesity (Roenneberg et al., 2012), metabolic syndrome (Parsons et al., 2015), and mental health disorders (Henderson et al., 2019), and notably lower

academic performance in high school students (van der Vinne et al., 2015; Zerbini et al., 2017; Zerbini and Merrow, 2017).

3.2 Position within a time zone

Time zones were introduced in the late 19th century to facilitate travel and communication between places of different sun times (i.e., local light-dark cycles). Ideally, time zones are centered around every 15th meridian such that a new time zone begins every 15 longitudinal degrees. The reason for this lies in the fact that the Earth takes 24 hours for one rotation, translating to a rotation speed of 15° per hour. Time zones may ease logistical challenges but create a discrepancy between social clock time and sun time: for a given time zone, social time remains the same but sun time changes systematically from east to west, with a 4-min delay in sunrise per longitudinal degree. As a consequence, chronotypes are on average progressively later towards the west of a time zone (Borisenkov, 2010; Miguel et al., 2014; Randler, 2008; Roenneberg et al., 2004; Shawa and Roden, 2016), suggesting that the average level of circadian disruption may also be higher in the western parts of a time zone. Studies examining the assumption that health risks may be increased towards the western border of a time zone due to increased circadian disruption have reported a higher risk from east to west for total cancers combined and 23 specific cancers in a US population sample (Gu et al., 2017) as well as for cancer incidence, cancer mortality, and life expectancy at birth in population samples from Russia and China (Borisenkov, 2011). The findings suggest that circadian disruption is not only experienced by shift workers but that a certain degree also affects the wider population, with potentially broad implications for public health.

3.3 Daylight Saving Time

Daylight saving time (DST) and time zones are tightly coupled, since both can increase the discrepancy between social time and sun time. Roenneberg et al. (2019b) have argued that

“switching to DST is nothing else but assigning the respective location to one time zone further east”, thus further aggravating the east-west gradient of circadian disruption described above. The transition into DST creates a temporary “mini social jetlag”, since social time changes but sun time does not (changing at a much slower seasonal pace), increasing the discrepancy between them by one additional hour from one day to the next. Studies on DST and health and safety outcomes show (modestly) increased risks for, e.g., myocardial infarctions (Janszky and Ljung, 2008; Manfredini et al., 2018), ischemic stroke (Sipilä et al., 2016), and traffic accidents (Fritz et al., 2020).

3.4 Shift work

Adverse effects of shift work for health, safety and general well-being are well-documented, including cardiovascular diseases (Vyas et al., 2012), obesity and diabetes (Proper et al., 2016), and accidents and injuries (Fischer et al., 2017a). Shift work can involve (permanent) night shifts and/or rapid alternations of work times that span the 24-h day (e.g., rotation between morning, evening, and night shifts). Sleep-wake patterns in shift workers are often highly irregular, in response to these highly irregular work schedules. As previously described for sleep regularity in section 3.1, several co-occurring rhythms in shift workers are shifted and irregular, including sleep-wake behavior, meal timing, exercise, and light exposure, making it difficult to identify what ultimately drives the observed detrimental effects for health and safety. This is true for all CD proxies that we have briefly introduced here, which is both a strength and a weakness: they capture many aspects of CD and are thus useful predictors for a wide range of outcomes but are consequently non-specific.

Being the dominant zeitgeber for the circadian system, light has the power to both align and disrupt. With the adverse effects of circadian disruption beyond dispute by now, studies have focused on how light can be used to alleviate some of these effects. In the next section, we will

present an overview of the results, strengths, and weaknesses of studies that have used light interventions to reduce CD and/or mitigate associated adverse effects in the field. While including a wide range of ecological settings (i.e., hospitals, schools), we have put a special focus on occupational settings, where shift work is the dominant CD proxy and light interventions are more readily applicable and better understood than for other environmental causes of CD.

4 Field Studies: Using light to mitigate effects of circadian disruption in ecological settings

Carefully controlled, laboratory-based studies have demonstrated the efficacy of light interventions to shift circadian phase. Using the concepts of PRCs to light and principles of circadian entrainment described above, light interventions have been used to aid the adjustment of circadian phase to night shift hours and transmeridian travel (for review, see Burgess et al., 2002; Lowden et al., 2019). These studies have typically used DLMO or core body temperature minimum to assess the physiological shift in circadian phase. In addition, measurement of neurobehavioral factors such as alertness and performance across simulated night shifts has demonstrated that these important outcomes are improved when the circadian rhythm is in alignment with the relevant shift timing (Boudreau et al., 2013; Crowley et al., 2004). While these laboratory studies reinforce the potential for light as an intervention to shift circadian phase, the following section will focus on the translation of these findings to real-world environments.

In the field, light interventions have been trialed with the aim to improve performance and alertness through adjustment to shift work, especially night shifts. Light during the day has also been used to help improve daytime alertness and nighttime sleep quality. This section will look at both the phase shifting and acute alerting properties of light across a variety of real-world settings from schools, to hospitals (patients and staff), and space missions.

Finally, compared to controlled laboratory experiments, field studies highlight the multitude of confounding factors influencing the success of lighting interventions across a range of ecological settings. We will address these challenges and make recommendations for future field research at the end of this section.

4.1 Phase shifting effects of light

There are mixed results from field studies as to whether light interventions can effectively shift circadian phase, improve alertness and performance outcomes on shift, and improve sleep quality during the day. The protocols vary widely across settings, shift type, intervention specifications (type of light and exposure duration/timing), and outcome measures, making it difficult to directly compare across studies. Reviews of the literature, however, have highlighted the relative success of these interventions despite the variety of approaches and contexts (Lowden et al., 2019).

In studies in which bright light was administered across the duration of the night shift, modest improvements have been observed such as mitigating the decrease in performance across the night shift and improving subjective alertness (Czeisler et al., 1991; Sletten et al., 2021). However, a recent study investigating the rate and severity of hospital errors committed under different lighting conditions found no significant difference in error rates between conditions (Chen et al., 2021). Despite the large sample size of over 1000 intensive care unit (ICU) admissions, the study may have been underpowered to detect a difference in this novel, but important, outcome measure. Alternatively, the challenges in implementing the lighting intervention and inability to control external factors contributing to error rates may have also obscured any meaningful effect of the light intervention.

To meet the challenges of different operational environments, some studies have trialed intermittent exposures to bright light during a shift or, where the operational context further limits light exposure at work, using light outside of work hours at home. It is important to test the efficacy

of these alternative intervention approaches as different workplace settings will have different logistical requirements. For example, while a factory may be able to upgrade their entire overhead lighting in the room that workers spend the majority of their time, in hospital settings, designated break rooms which are only frequented periodically may be the only option. In other settings, personalized light interventions such as light boxes or light-emitting glasses may be more appropriate. Short bouts of exposure to bright, blue-enriched light during a night shift, and/or at home before work appears to also be effective in improving subjective reports of alertness, mood, performance, sleep, and circadian adjustment to night shifts (Aarts et al., 2020; Barger et al., 2021; Olson et al., 2020; Stewart et al., 1995).

It should be emphasized that light intervention studies seldom include the addition of light exposure alone. Instead, light exposure is often combined with sleep hygiene advice, light avoidance schedules, and, in some cases, other interventions (e.g., exercise; Barger et al., 2021). These added interventions may be critical to the success of the lighting intervention and cannot be disentangled from the direct effects of the light exposure itself. With regard to light avoidance schedules, some studies also provided or recommended the use of sunglasses, goggles, or blue-blocking glasses during the morning hours which coincided with the end of their shift (Aarts et al., 2020; Olson et al., 2020; Stewart et al., 1995). Figure 4 shows an example light exposure and light avoidance intervention approach to adjust to a night shift by delaying circadian phase. Avoiding light, and especially short-wavelength light, during this time reflects the tenets of the PRC approach such that light exposure in the morning may offset the phase delaying impact of the light exposure at the start of the shift and across the night. It is worth considering, therefore, whether bright light exposure across an entire night shift (e.g., 7pm-7am) may also have canceling effects with the light later in the shift promoting an offsetting phase advance. These different approaches have not yet been directly compared in a field setting.

The other aspect to weigh up when choosing a light protocol, however, is the acute alerting effect of light. For instance, if the workplace was suddenly dimmed after an arbitrarily determined “mid-circadian point” of, say, 4am, workers may feel sleepier and have impaired performance in the second half of the night when they need the most stimulus to offset the circadian low in alertness and high homeostatic drive for sleep. Similarly, there is some controversy of the use of sunglasses when driving home given the already high incident crash risk for drivers commuting from a night shift (Australian Bureau of Statistics, 1997; Jackson and Moreton, 2013). Here, the benefits of light avoidance to improve recovery day sleep may not outweigh the need for an alerting stimulus on the drive home to reduce the risk of a drowsy related accident.

Overall, light interventions designed to help shift workers adapt to night shifts in the field appear to provide modest improvements to alertness, performance, and sleep quality, but findings are less robust and less consistent than laboratory studies due to other influencing factors.

----------Insert Figure 4 here----------

4.2 Zeitgeber strengthening and acute alerting properties of light

Several field studies have also assessed the use of light during the day to improve daytime alertness and nighttime sleep. Again, the setting, population, outcomes of interest, and intervention approach vary greatly across studies. For many of these interventions, the target population lives or works in settings which limit the amount of natural daylight exposure, and often have artificial light exposure at night. The combination of low light levels during the day (typically indoor lighting), and greater than zero levels at night dampens the strength of light as a zeitgeber. For example, in hospitals and care homes in which patients are not mobile and have little opportunity to go outside, or reside in windowless rooms, enhancing daylight exposure or providing brighter, blue-enriched artificial light is proposed to increase zeitgeber strength, thus

strengthening the entrainment signal of the circadian rhythm. This, in turn, can help to promote consolidated sleep at night, and alertness during the day. Light has also been shown to have direct, acute alerting effects (for review, see Lok et al., 2018; Souman et al., 2018).Thus, bright light exposure during the daytime may have two mechanisms of action: both acute and circadian.

In studies assessing constant bright light exposure across the daytime, Viola et al. (2008) trialed blue-enriched lighting in an office setting with exposure throughout the work day. Only subjective measures were assessed, but nearly all outcomes were improved from alertness and mood, to self-rated performance and concentration, as well as eye discomfort and sleep quality. Hopkins et al. (2017) sed a similar lighting intervention in a care home and found that while daytime activity levels were increased and anxiety was reduced, sleep outcomes were worsened, and rest-activity rhythms were advanced under the blue-enriched lighting condition. In this setting, residents of the care home were able to freely move about the home. The authors hypothesized that habits of residents – to spend morning hours in the common spaces where the light intervention was in effect and return to dimly lit bedrooms in the afternoon - may have caused this advance in circadian rhythms and subsequent nighttime sleep disturbances. Therefore, while the light settings in both of these studies were static, exposure to the light varied across the day based on behavior which resulted in different outcomes. Similar problems are encountered in classroom settings, as student schedules vary after morning homeroom, leading to different light exposures throughout the day. Consistent morning light exposure, however, may be most effective for these adolescent populations with a tendency for a later chronotype. Indeed, morning light has been shown to improve cognitive outcomes with long-term application in classroom settings (Keis et al., 2014).

In contrast to static lighting conditions, some studies have employed “dynamic” lighting approaches in which light at dawn and dusk are modified to better reflect the natural daylight cycle. In these dynamic lighting protocols, the color of the light typically changes from short-

wavelength bright blue light in the morning and through the day, changing to dim, longer wavelength light (lower color temperature) in the evening for the few hours before bedtime, as well as dimming of nocturnal light to as low as possible. The aims of this lighting protocol are to promote alertness during the day, avoid circadian phase delays due to bright light exposure in the evening hours, and promote consolidated sleep during the night. This lighting protocol can also be used to help entrain circadian rhythms in environments in which there is insufficient light to entrain to, from windowless workspaces through to the International Space Station. In hospital settings in which patients are relatively immobile, exposure to biodynamic intervention lighting has shown high compliance and modest improvements to sleep outcomes have been reported (Giménez et al., 2017; van Lieshout-van Dal et al., 2019).

Installing dynamic lighting may be a costly venture. Studies that simply manipulate home lighting or observe differences across seasons with natural changes to daylight exposure offer insight into how small differences may also lead to changes in sleep and wellbeing. For example, Burgess & Molina (2014) manipulated lighting in the evening using only the lighting already existing in participants' homes. No intervention lights were provided. For 4 hours before bedtime, participants were asked to dim their home lights and wear blue-blocking glasses or to use normal indoor lighting during this period. The maximum illuminance measured in the "bright" light condition was 65 lux. Even under these unremarkable conditions, DLMO was delayed ~1 hour in the normal light setting compared to dim setting. In a study across seasons, higher exposure to natural morning light in winter was associated with better sleep quality and circadian entrainment (Figueiro et al., 2017). Interventions, seasonality, and access to natural light can also interact such that interventions are less effective when daylight exposure is high, but can be helpful to augment natural light in winter or in cases where natural light is inaccessible (Vetter et al., 2011).

4.3 Non-24-hour light-dark cycles

Space exploration has driven a considerable amount of research into light interventions to promote adaptation to unusual shift patterns and light-dark exposures. Space travel presents numerous challenges to sleep and circadian entrainment including environmental factors such as noise, light, temperature, shift schedules requiring extended hours, fast transitions, high workload and stress, insufficient entrainment cues due to poor lighting and non-24-hour light-dark cycles, and the relatively unknown influence of micro-gravity, confinement, and isolation (Brainard et al., 2016; Mallis and DeRoshia, 2005). The need for astronauts to perform at their best in high stakes environments drove a flurry of research in the 1990s, with several studies conducted to investigate the most efficient way to switch to night shifts in order to maintain alertness and performance on shift. A workshop on this topic concluded that regardless of the rate of adaptation to night shifts, light interventions accelerated the process (Santy et al., 1994).

While humans have evolved to entrain to the Earth's 24-hour light-dark cycle, space exploration presents new challenges as we move away from Earth itself. On the International Space Station, orbiting the Earth creates a sunrise and sunset every approximately 90 minutes, creating ultra-short light-dark cycles which, when combined with windowless working areas, presents a challenge for entrainment. Dynamic lighting to mimic the Earth's dawn, midday, and dusk may help astronauts entrain to a 24-hour light-dark cycle while in orbit.

Studies have also investigated our ability to adapt to non-Earth day lengths such as the Martian day (called a Mars sol, 24.65 h). Barger et al. (2012) had the opportunity to implement a fatigue management program to support Phoenix Mars Lander mission personnel operating shift schedules anchored on a Mars sol. The program consisted of sleep and fatigue education and trialed a blue-light intervention using light boxes at workstations. Nearly all (87%) of those treated with the blue-light intervention adapted to the new light-dark period and achieved approximately one hour more sleep when synchronized to the new day length. Workers who did not participate

in the fatigue management program reported worse outcomes in terms of fatigue and difficulty of working on a Mars day. However, some participants who did not use a light box also adapted, so it is unclear how much the light contributed to adaptation relative to the sleep education or whether those who adapted perhaps had naturally longer circadian periods. This study highlights the flexibility of the human circadian system, and the potential impact of light in assisting entrainment to non-24-hour light-dark environments.

4.4 Challenges and recommendations

In controlled laboratory studies, participants are typically thoroughly screened homogeneous samples, exposure to the light intervention can be enforced, other light sources can be extinguished, and compliance with the protocol can be maintained. In field studies, and indeed in real life, there are many challenges to implementing interventions and even more confounding variables influencing the measured outcome. Below we discuss some of the challenges to translating promising light interventions to the field and provide recommendations for future research.

4.4.1 No one-size-fits-all

The challenges experienced in various occupational, educational, and home settings will vary such that a one-size-fits-all approach is not viable. Studies describing light intervention trials in a variety of ecological settings do, however, allow insight into many unforeseen challenges, and highlight a range of solutions that may be adapted or translated to other settings. For example, while the challenges of implementing changes in spaceflight may differ greatly to a chemical plant, the ability to have almost complete control over an astronaut's day during pre-flight quarantine may result in similar solutions to immobile patients in a hospital setting. For occupations in which workers are more mobile, or there is less control over light during non-working hours, fixed lighting in a designated space may not be sufficient, and more personalized exposure or shorter, targeted

intervals of exposure may be a better option. An assessment of the operational constraints and lighting solutions available before implementation will help to increase the chance of a successful intervention.

4.4.2 Assessing compliance to the protocol

When assessing the efficacy of an intervention in the field, care must be taken to design a study which is able to measure the compliance with the protocol and exposure to the intervention. Self-report may provide a rough estimate of this exposure, but a light sensor is a better measure. A sensor worn as close to the eye and angle of gaze as possible is preferred, for example, a sensor on glasses or worn as a pendant. Assessing compliance and exposure can provide important information about the viability of an intervention. If compliance and exposure is found to be low, this is not a failure of the study per se, but rather exposes barriers which require solutions to improve viable implementation. For example, an intervention in which bright, blue-enriched overhead lighting is installed may not be successful if the workers all wear hats with a front brim. Even well-designed studies can run into unforeseen problems which can serve as learning opportunities for future interventions.

4.4.3 Using and reporting recommended light settings

The type of light used, as well as the relative exposure to the light source, is critically important to the success of any intervention. Further, properly reporting the metrics of light interventions is crucial for others to interpret the results and to be able to replicate studies. A consensus of circadian and light experts is set to be published which provides recommendations for light levels needed to promote good health (Brown et al., 2020). The recommendations focus on indoor lighting levels required across different times of day for people living on a regular schedule in line with the natural light-dark cycle, but lessons can be learned for interventions directed at shift working populations. The authors recommend that the melanopic equivalent daylight (D65)

illuminance is >250 lux during the daytime; <10 lux 3 hours before bed; and <1 lux at night. These light levels are recommended using established metrics compliant with International System of Units (SI) standards (Commission Internationale de l'Eclairage, 2018). This document is a state-of-the-science guide that should be followed in all future circadian and acute alerting lighting interventions to report light metrics reflecting sensitivity to non-visual ocular systems.

4.4.4 Considering visual aspects of light

As sleep and circadian scientists, we must acknowledge that our approach to light is predominantly from a non-visual perspective. There are many disciplines, however, with competing interests and important knowledge about lighting such as visual comfort, interior design, and energy efficiency. Several studies concentrate on these factors in qualitative approaches which fall outside the remit of this chapter. However, just as we exclude these studies as they do not include circadian or alertness measures, so too may others overlook circadian studies if the qualitative experience of lighting is not measured. Instead, studies should aim to incorporate a range of measures and work with interdisciplinary teams. Further, the visual experience with regard to safety is incredibly important for human factors design of indoor spaces. For example, light that is dimmed to improve the sleep of inpatients may be too dim to accurately distinguish between pharmaceutical pills or to check infusion lines (Aarts and Kort, 2017). Light of a certain color may make it difficult to interpret warning lights on system displays and monitors, or glare from bright lights may reflect and obscure vital information. Therefore, careful consideration of the impact on physiology, qualitative experience, and human factors design is needed when implementing and assessing lighting interventions.

4.4.5 Weighing up short-term and long-term benefits

When considering the best approach to lighting interventions at night, consideration must be given to the overall shift schedule of the workers. If employees only typically work one night shift in a

duty block, attempting shifting circadian rhythms may make it more difficult to obtain recovery sleep at nocturnal times after a night shift. In addition, exposure to light at night during a period in which melatonin would naturally be secreted is associated with a range of negative long-term health outcomes such as metabolic disease, heart disease, immune suppression, mental health, and cancer (Lunn et al., 2017). On the other hand, sleep loss due to circadian misalignment during night shifts has also been associated with poor health outcomes. Further, in some instances, the need for visual clarity or optimum alertness during a night shift in safety-critical workplaces may outweigh any potential long-term health risks. The exact mechanisms underlying long-term health outcomes are not yet known and further research is needed to provide best practice guidelines on the tradeoff between short-term and long-term costs and benefits.

4.4.6 Tailoring light interventions to individuals

Another balance to strike is whether to apply a lighting intervention at a group or individual level. Given that the timing of light exposure is critical with regard to phase shifting, personalizing light interventions may be a more appropriate option. However, rapidly and cheaply assessing individual circadian phase is also difficult and albeit faster and less expensive methods are being developed (e.g., Wittenbrink et al., 2018), they are currently not field deployable in large numbers. Models developed to predict individual circadian phase in the field are, therefore, of great interest (Stone et al., 2020). While current models have shown success in predicting circadian phase in individuals with regular sleep/wake schedules, the accuracy of predictions under shift work conditions is also improving (Knock et al., 2021; Postnova et al., 2014, 2013).

5 Conclusion

Light is the predominant zeitgeber to entrain the human circadian clock. Disruptions to the circadian system can be caused at several levels, including a mismatch between self-selected

light-dark cycles and the environmental day-night alternation. Such a mismatch can be induced by external factors, e.g., shift work, daylight saving time, and position in a time zone, which have been used as proxies of circadian disruption to study effects on health and safety outcomes in the field. The adverse impacts of circadian disruption are well-documented, giving rise to a body of research that addresses the use of light interventions in the field to mitigate and minimize these effects. While some degree of control in field studies in early concept and translation phases of intervention testing is warranted, ultimately these interventions need to be robust enough that they are effective across broad populations, under various situations. Following guidelines to measure the compliance rate, install recommended lighting, and report successes and failures for others to learn from will ultimately move this area of research forward to better support shift workers and others in ecological settings which lead to misalignment with an imposed or self-selected light-dark schedule.

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Figure legends

Figure 1. Schematic phase response curve (PRC) to light. CBT_{min} = core body temperature minimum (in this example, 5:00).

Figure 2. a) Distribution of human chronotypes, based on the timing of midsleep on weekends. **b)** Relationship between chronotype and age by gender. Data from the American Time Use Survey (ATUS, n = 53,689). Adapted from: Fischer et al., 2017b.

Figure 3. Proxies of circadian disruption (CD) in ecological settings. The raster plots in panels a, c, and d show sleep-wake patterns exemplified for different CD proxies, where black bars = sleep, blue shading = solar night, yellow shading = solar day. DST = Daylight saving time. ST = Standard time.

Figure 4. Example of a gradual phase-delay strategy with bright light exposure and light avoidance.

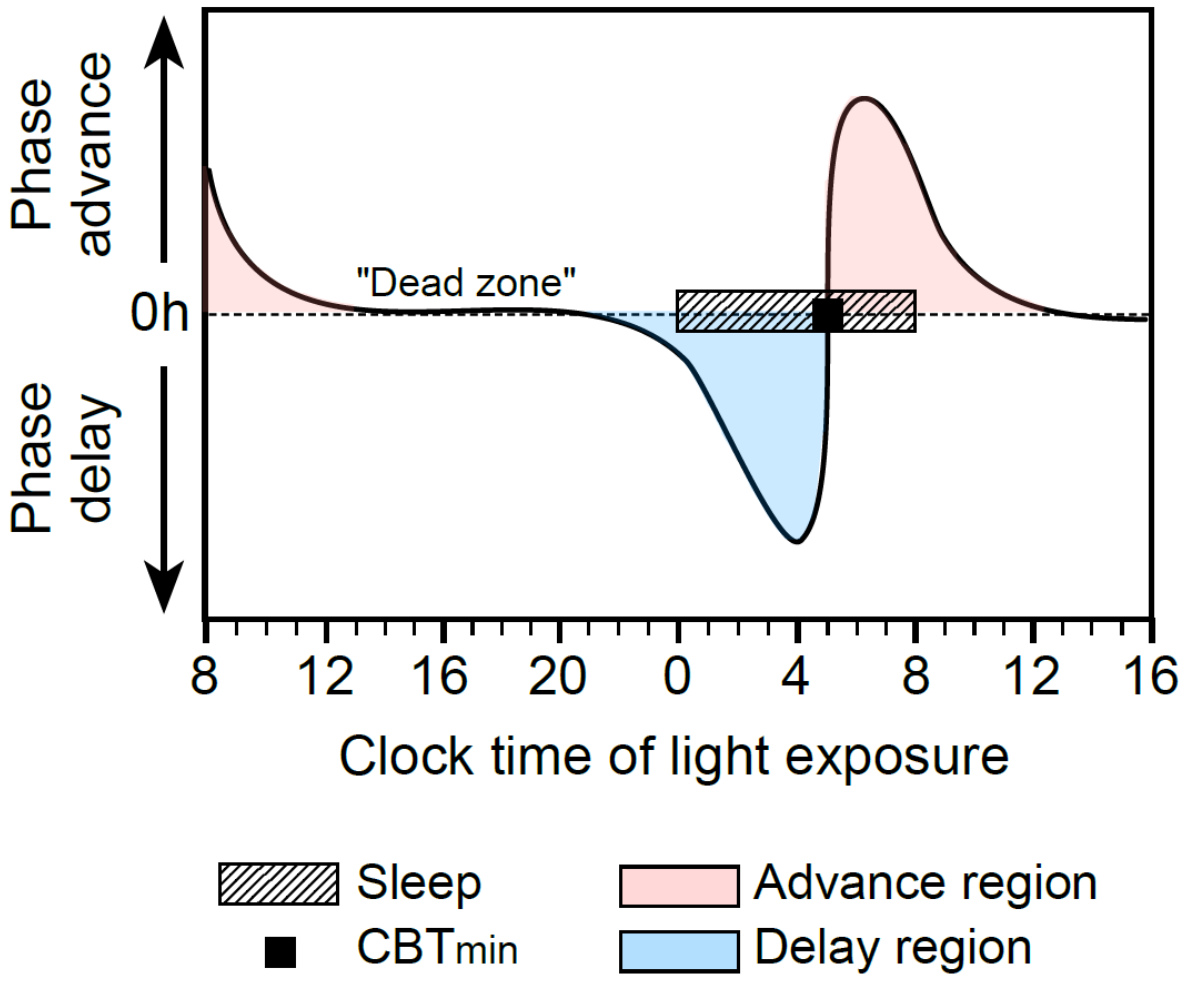
Phase advance
0h
Phase delay
"Dead zone"
8
12
16
20
0
4
8
12
16
Clock time of light exposure
Sleep
CBTmin
Advance region
Delay region

Figure 1.

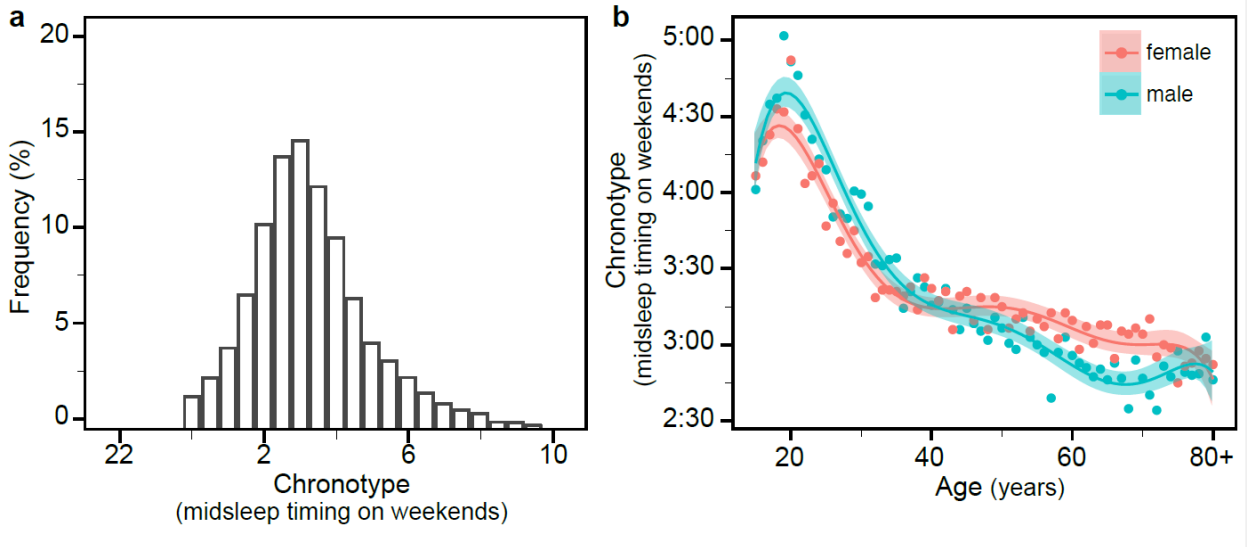
a
Frequency (%)
20
15
10
5
0
22
2
6
10
Chronotype
(midsleep timing on weekends)
b
Chronotype
(midsleep timing on weekends)
5:00
4:30
4:00
3:30
3:00
2:30
20
40
60
80+
Age (years)
female
male

Figure 2.

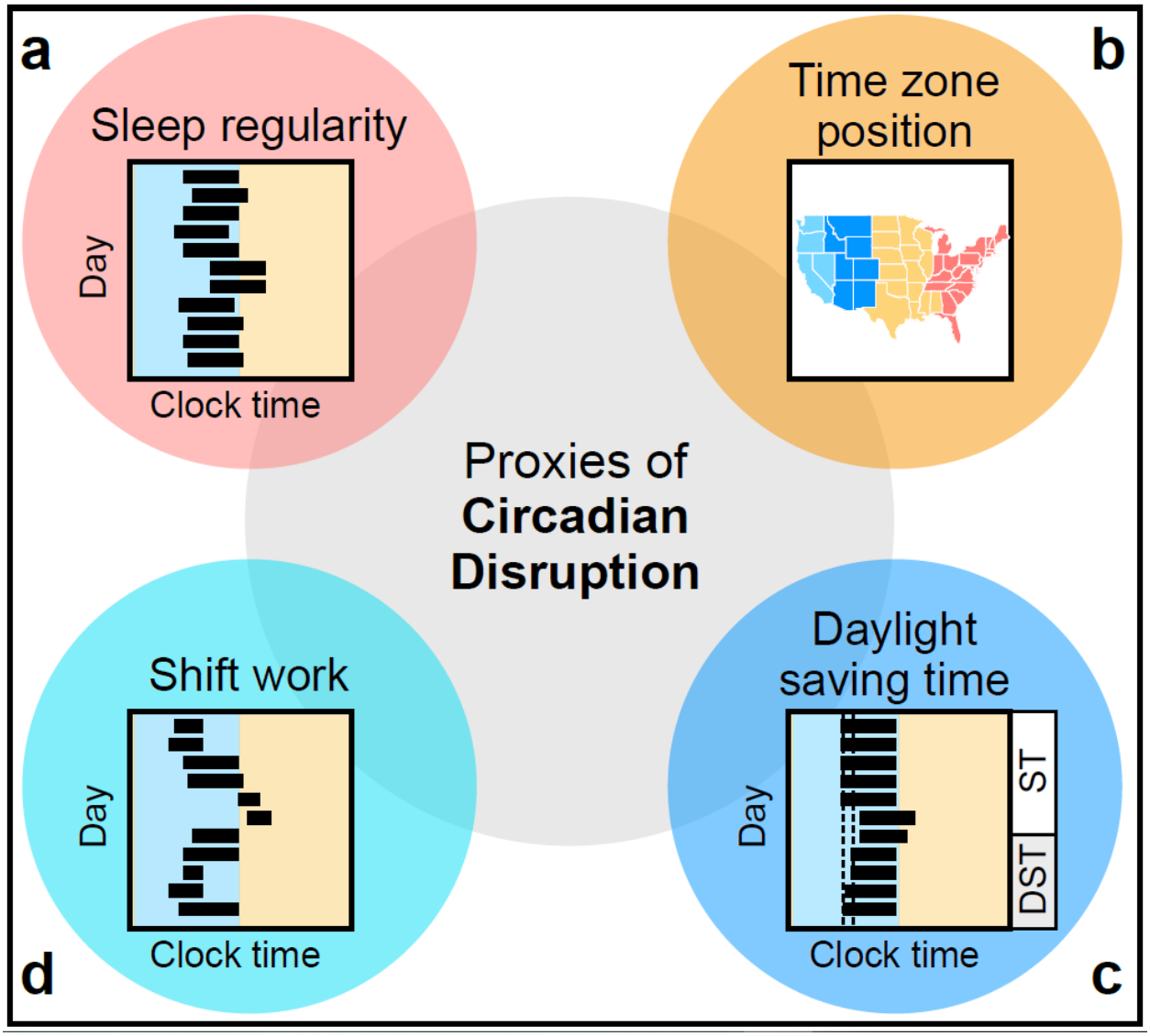
a
Sleep regularity
Day
Clock time
b
Time zone position
Proxies of
Circadian
Disruption
d
Shift work
Day
Clock time
c
Daylight saving time
Day
ST
DST
Clock time

Figure 3.

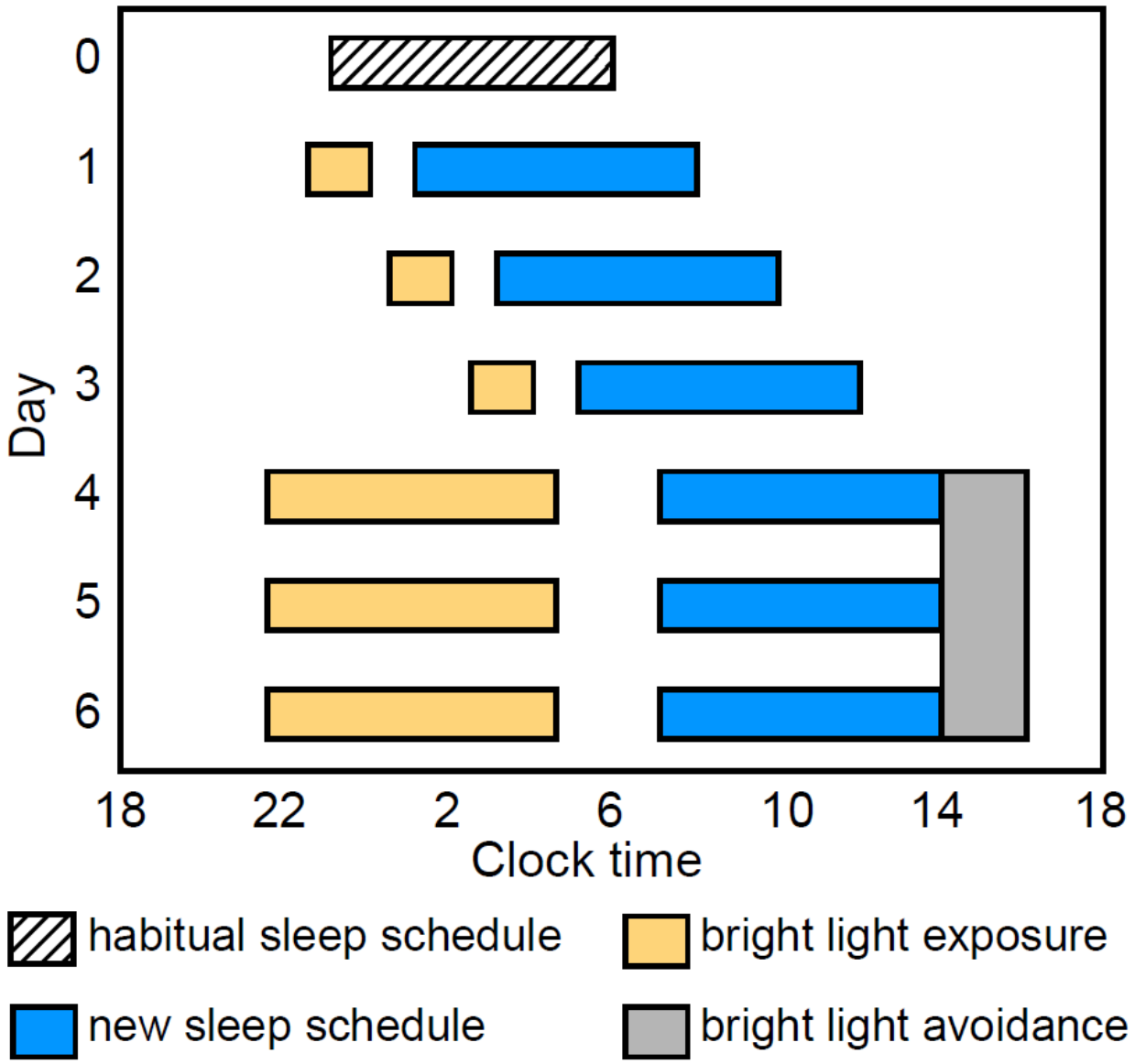
0
1
2
3
4
5
6
Day
18
22
2
6
10
14
18
Clock time
habitual sleep schedule
bright light exposure
new sleep schedule
bright light avoidance

Figure 4.