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► To cite this version:

Jacques Taillard, Patricia Sagaspe, Pierre Philip, Stephanie Bioulac. Sleep timing, chronotype and social jetlag: Impact on cognitive abilities and psychiatric disorders.. *Biochemical Pharmacology*, 2021, 191, pp.114438. 10.1016/j.bcp.2021.114438 . hal-04099948

HAL Id: hal-04099948

<https://hal.science/hal-04099948v1>

Submitted on 22 Jul 2024

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Sleep timing, chronotype and social jetlag: impact on cognitive abilities and psychiatric disorders

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Key words: Sleep timing, morningness-eveningness, chronotype, social jetlag, cognition, mood disorder, ADHD

Abstract

Sleep timing is controlled by the subtle interplay between circadian and homeostatic oscillators which, according to their endogenous properties, allow beings to feel spontaneously that it is time to go to bed or wake up in synchrony with the earth's light/dark cycle. In humans, however, social time and nocturnal artificial light modify sleep timing. Our modern lifestyle and artificial nocturnal light delay our bedtime, make us wake up, and lead to a greater intraindividual variability in sleep timing. Depending on the constraints that social time places on us, our sleep timing may be in or out of phase with the internal circadian timing determined by the circadian clock. When a person's social time is out of phase with their circadian time, they may be considered to suffer from circadian disruption or 'social jetlag'. There are interindividual differences in sleep timing that are known as morningness-eveningness preferences or chronotype, e.g. late chronotypes go to bed later. Chronotype may be assessed in terms of differences in kinetic homeostatic sleep pressure, intrinsic circadian period (ICP) and/or phase angle entrainment. In addition, chronotype depends on genetic and age-related factors, e.g. it gets earlier as people grow older. The social time of late chronotype individuals during week days is not adapted to their circadian time, unlike on free days. This results in social jetlag and circadian disruption, which in turn induces a chronic sleep debt due to a late bedtime and an early wake time, which is compensated on free days but only partially. Sleep and circadian clock disruption generally alter cognitive performance (alertness, attention, memory, higher-order executive functions such as response inhibition and decision-making) but their impact remains to be clarified. When subjects adopt their preferred sleep timing, a "synchrony effect" often appears with chronotypes performing better during daytime at optimal than at suboptimal timing (late chronotypes perform better in the evening, early chronotypes in the morning). Evening

types appear to be cognitively more vulnerable to suboptimal times than morning types, probably because they have to deal with social jetlag and the “wake effort” period after awakening. Circadian disruption, but not chronotype, may impact attentional/inhibitory performance (more impulsivity and inattention). Strong associations have been found between mood disorders or attention deficit hyperactivity disorder (ADHD) and chronotype, with these psychiatric disorders typically being overrepresented in evening types. The association between social jetlag and these psychiatric disorders is less obvious. Social jetlag can be corrected by reducing exposure to evening light, although eveningness may be considered as a lifelong factor predisposing to depression or inattention.

In humans, sleep timing is controlled by an interaction between the circadian and homeostatic oscillators which dictate spontaneous bedtime and wake time in phase with the earth's light/dark cycle [1]. In fact, our decision to go to sleep or to wake up depends mainly on our social activity. Contrary to animals, human beings have quickly adapted their sleep timing according to their abundant social activity. Although humans are diurnal beings active during the day and asleep at night, the domestication of fire (campfires in pre-industrial societies) and then the discovery of artificial light allowed them to extend the photophase and reduce the scotophase, thereby allowing them to enjoy family, social and leisure activities in the evening. Social activities in the evening made possible by artificial light, together with the proliferation of electronic devices and social communications in many forms, have delayed our bedtime.

Wake time is spontaneous and associated with dawn in pre-industrial societies [2]. On the other hand, modern industrialized societies have led to the emergence of two factors that have significantly modified wake time and its regularity: working hours and rest days (Sunday rest and, more recently, Saturday/Sunday rest or Friday/Saturday in most countries). In fact, most of us wake up well after dawn and use an alarm clock to be sure that we get to work on time. In addition, the modern lifestyle and artificial light allow us to live indoors more often, thus depriving us of natural light during the day. Depending on our social time, our sleep timing may be in or out of phase with the internal circadian timing determined by the circadian clock. The phenomenon of social time being out of phase with biological time is known as circadian disruption or social jetlag. In addition, sleep timing is known to vary across individuals. Sleep/wake regulation presents trait-like dimensions relating to circadian and homeostatic characteristics that inevitably induce an inter-individual difference known as morningness-eveningness preference or chronotype. First,

we review the basics of circadian rhythm, rhythmicity, and sleep wake regulation in order to better understand the concept of social jetlag. Then, we examine the relationship between chronotype and social jetlag and the impact it has on cognitive abilities and psychiatric disorders.

Sleep timing: interaction between circadian and homeostatic drive

Sleep timing is controlled by two internal oscillators: the circadian and homeostatic oscillators [1]. During the biological day, the circadian oscillator generates a drive for wakefulness whose intensity is maximal at the end of the day close to the onset of melatonin secretion. This maximal circadian drive for wakefulness is termed the “wake maintenance zone” or “forbidden zone of sleep”. Thereafter, the drive for wakefulness dissipates rapidly to make way for the drive for sleep, which reaches its maximum at the end of the night close to the core body temperature minimum. When drive for sleep dissipates, the propensity to wake up appears.

In mammals, the circadian oscillator is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [3], also called the biological clock. The SCN displays circadian rhythms in electrical activity and a firing rate over 24 h, with high activity during the day and low activity during the night. In humans, the biological clock has an endogenous rhythmic property (internal time cue) and oscillates with an intrinsic period that is slightly longer or shorter than 24 hr (free-running period) [4]. The molecular principle of cellular circadian rhythmicity is driven by interlocked transcriptional/translational feedback loops composed of a subset of clock-related genes. Two transcriptional factors are situated at the core of the loops: the BMAL1 and CLOCK proteins. In the morning, they form a protein heterodimer that activates the transcription of the PER (1,2,3), CRY (1,2), ROR β and REV-ERB α proteins. PER and CRY

proteins accumulate in the cytoplasm during the latter part of the day and the early part of the night. Then, after nuclear translocation, PER and CRY inhibit the transcriptional effects of CLOCK-BALM1 during the rest of the night and thus exert negative autoregulation of their own transcription. The negative feedback results in circadian expression of PER and CRY transcription. Additional regulatory loops involving the REV-ERB α and ROR γ proteins inhibit or activate the transcription of BALM1. CLOCK-BALM1 drives the transcription of several clock-controlled genes that induce circadian rhythmic cellular-molecular process to lead to complex circadian behavior.

It is important to understand that a polymorphism of the clock gene induce changes in the intrinsic period. A short intrinsic period is thought to be linked to a fast biological clock and thus to an early circadian phase (localization of maximum or minimum of circadian rhythm,) while a long intrinsic period is thought to be linked to a slow biological clock and thus to a late circadian phase. Because the intrinsic period is not exactly 24hr and to be able to function in harmony with the geo-physical environment and allow the daily rhythms of behaviors and physiological processes to be optimized, the biological clock is reset every day and is entrained by what are known as zeitgebers, i.e. external time cues [4]. The signals (biological rhythms) generated by the entrained biological clock are considered to be circadian time, which is different from social time. The most important zeitgebers are photic zeitgebers like the light/dark cycle [5]. In humans, photic zeitgebers are the natural day's sunlight and night's darkness but also exposure to artificial lighting like electrical lighting, screens, etc. Light signals are detected by the retina [6], especially the rods, cones and the melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) [7], and are transmitted to the biological clock via different pathways [8]. Depending on the time at which it is received, the light advances (in early morning) or delays (in late evening) the

biological clock according to a phase response curve [9]. To maintain steady-state entrainment at 24 h in a person with an intrinsic period of more than 24 hours, the clock must be advanced by light every day. In other words, the longer the intrinsic period, the greater the ratio of phase advances to phase delays (in accordance with phase curve response more light on the advance of zone, and less light exposure on the delay zone) and vice-versa. In real-life conditions, the biological clock must be driven by zeitgebers and must establish a stable phase relationship with them that is known as the phase of entrainment [10, 11]. The phase of entrainment describes how the clock is aligned with the light-dark cycle. The phase angle of entrainment is the time difference between internal time, expressed by the phase of the biological clock (timing of cycle, i.e. temperature acrophase or dim light melatonin onset), and external time, expressed by the phase of zeitgeber, i.e. dawn for light/dark cycle. The phase of entrainment depends on the intrinsic period of the biological clock, the strength of the zeitgeber and the sensitivity of the biological clock to the zeitgeber. As the light/dark cycle is not fixed in humans, the phase angle of entrainment is usually taken to be the time difference between the phase of the biological clock and sleep timing (bedtime, wake time or mid-sleep time) [12]. This estimation is correct only if the sleep timing accurately corresponds to the timing of the light/dark cycle [12]. This phase relationship is important because it provides information about the length of the intrinsic period [11]. For example, a person with a long intrinsic period will not only have a late circadian phase but will also be entrained with a shorter phase angle (shorter interval between minimum body temperature and wake time) and vice versa. Excessive sensitivity to light will amplify the entrainment effect and thus modify the phase angle. People with greater sensitivity to light have a shorter phase angle.

The homeostatic oscillator triggers a homeostatic drive that corresponds to the physiological need for sleep, known as homeostatic sleep pressure, which increases during wakefulness and dissipates during sleep [13]. The sleep factor that builds up in the brain during wakefulness and dissipates during sleep is not clearly identified. Perhaps the best candidate is adenosine, which increases in the basal forebrain during time awake and dissipates during sleep and has been proposed to account for the action of adenosinergic drugs such as caffeine on sleep onset [14, 15]. Adenosine, via A1 receptors, inhibits wake-promoting cholinergic neurons in the basal forebrain and increases sleep-promoting GABA neurons in the sleep-active ventrolateral preoptic nucleus (VLPO) via A2 receptors. Homeostatic drive is governed essentially by sleep/wake behaviors and depends on a person's history of sleep. The intensity of sleep pressure depends on the duration of prior awakening. High intensity exercise, but not moderate exercise, affects brain energy metabolism by accumulation of adenosine from ATP breakdown [16] and may also play a key role in homeostatic sleep regulation. Homeostatic drive also plays an important role in sleep timing [17] and is thought to be a use-dependent process reflecting changes in plasticity [18].

Sleep timing depends on the interaction between circadian and homeostatic oscillators [1, 19, 20]. During a normal day, the buildup of sleep pressure is counteracted by the circadian drive for wakefulness, especially during the wake maintenance zone, in order to extend the period of wakefulness. After this specific zone, the combination of higher homeostatic drive and rapid dissipation of circadian drive for wakefulness leads to the propensity to fall asleep. After sleep onset the rapid dissipation of homeostatic drive is counteracted by the circadian drive for sleep in order to extend the sleep period. The dissipation of the circadian drive for sleep combined with the dissipation of the circadian and sleep-dependent promotion of rapid eye movement (REM) sleep leads to the propensity to wake up. Homeostatic and

circadian drive interact to facilitate consolidated wakefulness throughout the day and consolidated sleep throughout the night. This consolidation of wakefulness and sleep is effective only if the circadian drive is strong enough.

Importantly, the homeostatic oscillator provides feedback to the circadian oscillator: the circadian amplitude depends on the intensity of sleep pressure, so the higher the sleep pressure, the lower the circadian amplitude. In other words, the circadian drive, especially the drive for wakefulness, is lower if sleep pressure is high. The activity of SCN decreases with increasing homeostatic sleep pressure [22]. The kinetic of the homeostatic oscillator also has an impact on the phase angle. During the same circadian phase, people with a slower accumulation of the S process will have a short phase angle [23].

There are other significant feedback pathways in this sleep wake regulation. Melatonin feeds back to the circadian oscillator and contributes to its adjustment to the light/dark cycle. Moreover, the onset of melatonin secretion is associated with the propensity to sleep [24, 25].

This two-process model has been complemented and extended by neurophysiologic data. For example, the Phillips-Robinson model [21-23] is based on the mutually inhibitory sleep-promoting VLPO (GABAergic) and the wake-promoting monoaminergic hypothalamic and brainstem neuronal populations (MA). The model produces flip-flop dynamics between sleep and wake, as driven by homeostatic/circadian processes and orexinergic neurons. During the day, circadian drive, produced by the SCN, inhibits VLPO and activates the orexinergic neurons of the lateral hypothalamic area (Orx). In the evening, circadian drive decreases, the strength of homeostatic drive is maximal, and this disinhibits VLPO which inhibits Orx and therefore inhibits MA, finally triggering sleep onset and stabilizing sleep episodes. At the end of the night, the strength of homeostatic drive is the lowest, VLPO is not activated, circadian

drive begins to inhibit VLPO and to activate Orx, and humans begin to wake up. This model posits that the dominant effect of the modifying period or amplitude of circadian drive is to change sleep timing, whereas the dominant effect of changing the kinetic of homeostatic drive is on sleep duration, with a slower build-up that tends to result in later bedtime rather than earlier wake time [15]. Orexin secreted during the day by the neurons of the lateral hypothalamus, which are networked with the SCN, contributes to consolidating wakefulness during the daytime [1, 21] in activating wake-promoting monoaminergic hypothalamic and brainstem neuronal populations (MA). MA includes noradrenergic neurons of the locus coeruleus, serotonergic neurons of the dorsal and median raphe nuclei, dopaminergic neurons of the ventral tegmental area and histaminergic neurons of the tuberomammillary nucleus. In fact, sleep timing may also depend on orexin levels, with higher orexin levels delaying the normal sleep episode [21].

Sleep timing: influence of social factors

In humans, social factors are one of the most important determinants of sleep timing. The strong influence of social timing on human sleep becomes apparent when comparing sleep-wake behavior on working and free days [24]. Usually, bedtime and wake time are determined by social time such as working hours, leisure time and our modern lifestyle, and not by the physiological regulation of the sleep/wake cycle. Due to the strong demand for social activities, the omnipresence of artificial indoor lighting and the development of communication channels (TV, smartphone, 4G, World Wide Web), we rarely go to bed at the first signs that the sleep gate is opening. Furthermore, some of us do not wake up spontaneously without an alarm clock at our preferred or circadian wake time because the

latter is usually dictated by social constraints such as school or work schedules. During the working day, sleep behavior in some people induces a transient and chronic misalignment between their imposed sleep timing and their endogenous circadian phase, commonly known as circadian disruption or social jetlag [25, 26]. Social jetlag is a proxy for circadian misalignment quantifying the discrepancy between social and biological time [27]. Social jetlag occurs when sleep timing on free days is close to the natural phase of entrainment or to the circadian wake propensity rhythm and when sleep timing under the “unnatural” time constraints of workdays are outside the natural phase of entrainment or the circadian wake propensity rhythm. Social jetlag may be defined as the difference between unconstrained and constrained sleep times, especially mid sleep time, and the concept is a good yardstick of “how much one lives against one’s biological clock” [25, 27]. In other words, it is the absolute difference between midsleep on free days and on workdays [25]. Midsleep is assessed by the Munich Chronotype Questionnaire [28]. More than 44% of the population suffer from 1 hours or more of social jetlag and 15% suffer from 2 hours or more [27]. Recently, Jankowski [29] proposed an alternative formula to assess social jetlag which excludes the effect of sleep debt. In this case, social jetlag is considered the absolute difference between sleep onset on free days and sleep onset on workdays [27].

One of the consequences of circadian disruption is that sleep duration is curtailed on workdays, mainly due to an early imposed wake time. Consequently, people do not sleep as long as recommended and may suffer from chronic sleep deprivation. As a reminder, the recommended sleep duration for adults and adolescents is 7-9hr and 8-10 hr, respectively [30]. Sleep debt is usually compensated for on weekends by longer sleep duration.

However, sleep duration in the night from Sunday to Monday is dramatically reduced due to a very late bedtime resulting from the phase delay incurred over the weekend associated by

an Monday early wake time due to social constraint: hence, the vicious circle of sleep debt may be perpetuated [31].

Sleep timing: influence of natural and artificial light/dark cycle

In addition to our modern sleeping behaviors, other factors amplify this circadian misalignment. First, social time (time for school, work or leisure) is largely regulated by local time. Local time is the time calculated by our watches/clocks which are set approximately to solar time (depending on the time zones). Time zones were created so the different regions of the globe could share the same notion of local time. Much of Europe has adopted the same time zone but there is a very large difference between solar time and local time depending on where you are. The closer to the western border of the time zone, the greater the difference between local time and solar time (i.e. in western Spain there is a difference of 90 minutes between local time and solar time). In the western part of the time zone, there is less early morning light exposure and more evening light exposure.

Secondly, since the introduction of indoor artificial lighting especially in the evening and exceptionally throughout the night, the period in which we are exposed to light is longer than the natural light/dark cycle. As seen above and in relation to the phase response curve of light, the introduction of light in the evening delays the onset of melatonin secretion and the circadian phase, leading to later bedtime. In addition, we spend a lot of time indoors so our exposure to light during the day is reduced, especially in the morning when circadian drive must occur. This under-exposure to light during the day results in the weakening of the photic zeitgeber, with the result that the phase of entrainment becomes later for most persons [32]. Using the Phillips-Robinson model, Skeldon et al. [31] modeled the effects of artificial evening light (40 lux) and social constraints on human sleep timing. Artificial

evening light delayed spontaneous sleep timing (without social constraints) but this phase delay does not modify the phase angle of entrainment (duration between wake time and minimum of circadian wake propensity, which is about 3 hr) [31]. On the other hand, the effect of artificial evening light was found to depend on the intrinsic circadian period: the longer the intrinsic period, the greater the effect of artificial evening light. The effect of evening light on sleep timing can be offset by a large increase in daytime light exposure [31].

When spontaneous sleep timing was modified by social constraints but in the absence of evening light, wake time occurred at 7 am on weekdays and at the weekend and the phase angle of entrainment was always 3 hours. On the other hand, when spontaneous sleep timing was modified by social constraints and when evening light was introduced, bedtime occurred later, and the phase angle of entrainment was much shorter. Sleep timing was out of phase with circadian rhythmicity on workdays. On rest days, sleep timing was even more delayed, sleep duration was extended to compensate for sleep deprivation on workdays, but the phase angle of entrainment was always 3 hr. On the other hand, during week end sleep timing are in of phase with the circadian rhythmicity [31]. Sleep timing differences between workdays and rest days were found to replicate the basic features of social jetlag.

Social jetlag also depends on other factors: the greater the social jetlag, the greater the circadian period and/or the lower light exposure during the day. Social jetlag is worse in individuals living on the western border of a time zone than in those in the east [31].

When sleep timing is modified by evening light exposure and social constraints, the wake time is close to the minimum of circadian wake propensity. As the circadian sleep drive is high at wake time, it requires effort to stay awake. In their simulation, Skeldon et al. [31] demonstrated that the “wake effort” lasts about 1.2hr.

Sleep timing: diurnal preference and chronotype

Interindividual differences in preferred behavior timing, especially in sleep timing, have been observed and confirmed. From the beginning of the 20th century (for history see [33, 34]), and in accordance with the diurnal preference for daily activity and sleep timing, humans are classified into groups: “larks” (early bird) and “owls” (night bird). This interindividual difference is usually named “diurnal preference”, “morning-evening type”, “morningness-eveningness” or chronotype. It follows rather a morningness-eveningness continuum. Larks (morning type) have a marked preference to wake up and to go to sleep early whereas owls (evening type) wake up and go to sleep late.

Morningness-eveningness is widely assessed by the Morningness-eveningness questionnaire [35] that we adapted according to the age of the person [36]. More recently, chronotype has been defined as the variability in phase of entrainment (which depends on intrinsic circadian period and strength of zeitgeber) [28]. The phase of entrainment is estimated by the mid-sleep on free days corrected for sleep debt accumulated during workdays (MSFsc) [37].

Chronotype is assessed by the Munich Chronotype Questionnaire (MCTQ) in calculating MSFsc. For a historical and critical review of morningness-eveningness or chronotype assessment, see [27, 34, 38, 39]. Even if there is a concordance between MEQ (morningness-eveningness) and MCTQ (phase of entrainment) [40], it remains to be verified and discussed whether the two questionnaires estimate the same dimension and/or preferential sleep timing behavior.

Most studies have found that the circadian phase of evening types is delayed by about 2 hours compared to the circadian phase of morning types [41-44]. This phase difference is thought to be related to a difference in the length of the intrinsic circadian period, evening types having a longer period than morning subjects [45], suggesting that morningness-

eveningness is trait-like. Mongrain et al. [46] observed that some morning types or evening types did not differ in circadian phase (overlapping phase or intermediate phase) despite having different sleep timing, while others had a large circadian phase difference associated with different sleep timing (non-overlapping phase or extreme phase). A difference in phase angle of entrainment between morning types and evening types was found [42] in a highly controlled experiment. The phase angle of entrainment is shorter in evening types and longer in morning types. These results have been confirmed by other studies [28, 41, 43, 47]. In other words, evening types wake up at a later local time but wake up at an earlier circadian time, and the opposite is true for morning types. As we have seen previously, a wake time close to the minimum circadian time will make subjects produce a “wake effort”. This “Wake effort” is used to determine morningness-eveningness in the MEQ. Mongrain et al. [46] confirmed this difference in phase angle entrainment only in morning types and evening types who presented the extreme phase. Concerning light exposure, morning types are more exposed to light in the morning while evening types are more exposed to it in the evening and at night [44, 48]. If the circadian phase is taken into account (as assessed by melatonin secretion onset or minimum circadian body temperature), morning types are more exposed to light later in circadian time (i.e. more light before melatonin onset), and the opposite is true in evening types. Thus, morning types have a high ratio of phase delay to phase advance by light and evening types have a high ratio of phase advance to phase delay by light (see paragraph: Sleep timing: interaction between circadian and homeostatic drives) [48].

We demonstrated that homeostatic drive, as assessed by the kinetic sleep pressure build up during the day, differs between morning types and evening types: morning types show a greater increase in sleep pressure during the day than evening types. In evening types, the

slower drive of the homeostatic oscillator with circadian phase delay can explain their later bedtime and wake time. Mongrain [49] confirmed these differences in the dynamics of homeostatic drive by studying dissipation of sleep pressure during sleep as assessed by slow wave sleep decay: dissipation of sleep pressure was faster in morning types than in evening types. This difference was observed only in chronotypes with intermediate phase. Mongrain et al. [46, 49] suggested that chronotypes with extreme phase have a different intrinsic period and that those with intermediate phase have a different homeostatic drive. In using their model, Phillips et al. [22] confirmed that chronotype depend on the relative influences of homeostatic and circadian drives, with a stronger homeostatic drive causing morningness. Preferential sleep behaviors have been observed in large cohorts of all ages [50-53]. As early as 1999, we showed that sleep behavior was different between free days and workdays and that it also depended on the chronotype. Evening types had a later bedtime and wake time especially at the weekend and built up a sleep debt during the week and slept longer at the weekend [50]. By introducing the concept of social jetlag, Wittman [25] demonstrated that social jetlag is greater in evening types and confirmed that late chronotypes showed the largest differences in sleep timing between work and free days, thus creating a considerable sleep debt on work days for which they compensated on free days. In late chronotypes, this social jetlag is essentially linked to their phase-delayed biological clock. In late chronotypes, the circadian sleep window occurs late after the onset of melatonin secretion.

We have seen above that artificial light amplifies the delay in the opening of the circadian sleep window, and that this effect is amplified in people with a longer intrinsic period (observed in evening-types). Before the waking time programmed by their biological clock, they are woken up by social constraints. This early wake time also requires a wake effort that lasts for a few hours after the wake time. The sleep duration of late chronotypes is

curtailed at both ends of the night. On free days they are able to recover the sleep timing imposed by their biological clocks while sleeping longer to compensate for the sleep debt accumulated during working days. It is interesting to note that the evening subjects consume more coffee than the morning subjects. Caffeine acts on the homeostatic pressure by decreasing it and on the biological clocks by lengthening the period and delaying the phase [54]. On workdays, late chronotypes go to bed late because the added effects of circadian drive, nocturnal artificial light and caffeine intake stop them from falling asleep earlier. On the other hand, in early chronotypes, social timing matches their circadian sleep timing, and they suffer little from social jetlag. In a recent analysis of 20 studies, Putilov et al. [55] showed that, on working days, morning types have the same sleep duration as evening types. They found that sleep lost on weekdays affects both chronotypes.

Chronotype depends on both genetic and oncogenic factors. Heritability of chronotype is estimated to be approximately 50% with some trait variance [56]. Studies in twin pairs and in population- and family- based cohorts have demonstrated a relationship between chronotype and polymorphism in CLOCK, PER1, PER2, PER3, BMAL and AANAT (involved in melatonin synthesis) genes [57]. However, these associations were not confirmed by other studies [57]. Multiple recent GWAS have identified many loci that show an association with chronotype [58]. Up to 351 loci, including PER2, PER3, and Cry1, have shown an association with chronotype in GWAS studies. This suggests that chronotype is attributed on basis of subtle differences in the biochemical feedback mechanism of the circadian clock. These GWAS studies found that an individual's chronotype is also influenced by variants in genes important in the correct formation and functioning of retinal ganglion cells (RGS16 and INADL), highlighting that some natural variation could be explained by better detection and communication (with the SCN) of external light signals. Variants in genes with a known role

in appetite regulation (FTO), insulin secretion (MADD) and even nicotine and caffeine metabolism (CYP2A6) have been also found [59]. It is widely accepted that the distribution of chronotype depends on age [50, 60], eveningness being associated with adolescence, peaking in the 20s and shifting toward morningness with increasing age [52, 53, 61, 62]. Additionally, there are gender-based variations in chronotype, with men generally having later chronotypes than women, most markedly during late adolescence and early adulthood. After the age 40-50 years, the difference disappears or even goes in the opposite direction [52, 53, 61-63]. All studies confirm that adolescents have on average the latest chronotypes. During adolescence, social jetlag is more severe especially in young men. In an adolescent German population, Randler et al. [64] found that social jetlag was nearly absent in young infants but then increased until age 17 years, where it reached 3:18 h, then gradually decreased. The authors suggested that the age around 16–17 years can be considered as a watershed point. Covering a period of 10 years, a study demonstrated that there were more evening subjects of any age and sex (25-74 years) in 2017 than in 2007, and especially in the age group 35-45 years [65]. However, in comparison with 2012, bedtime and midsleep during weekdays or weekend in 2017 were more advanced in young adults (25-34 years) and more delayed in older adults (65-74 years). Social jetlag was more pronounced in evening types but was less widespread in 2017 than in 2012.

In their model, Skeldon et al. [17] demonstrated that the later sleep timing during adolescence is explained by a reduction in circadian amplitude and homeostatic drive that then with age, the reduction in circadian amplitude dominates, resulting in progressively earlier sleep timing. By introducing nocturnal light into the model, they demonstrated that the later sleep timing observed in adolescence is largely a result of self-selected patterns of light exposure. On the other hand, sleep duration and phase angle of entrainment are not

modified by evening light exposure [31]. Leone et al. [66] studied the effect of lockdown related to the COVID-19 pandemic in 25,000 Argentinians (13-74 years). During lockdown, weekday sleep duration (+39 min, 61 % reaching the sleep duration recommended) increased and sleep schedules were delayed (sleep onset occurred 56 min later and sleep offset 1h35 later) especially in younger persons. On free days, sleep duration and sleep timing were not modified by lockdown. During lockdown, social jetlag was reduced (-54 min) and chronotype assessed by the MSFsc was delayed (+ 36 min), especially in younger persons. On weekdays, the use of alarm clocks and napping decreased during lockdown. This lockdown effect was observable only in participants who worked at home. Chronotype assessed by the MEQ did not change during lockdown.

These findings may be interpreted in two ways: either they are the effect of self-selected patterns of light exposure (less light in the day and more at night); or socio-professional constraints considerably modified the preferential sleep timing of the participants. The positive effect of lockdown on social jetlag and sleep duration has also been observed by others [67]. On the other hand, sleep quality decreased [67, 68] and insomnia symptoms worsened [69], especially in students and females. All of these studies suggest that the positive effect of lockdown on social jetlag and sleep duration was cancelled out by the effect of social isolation and the feeling of loneliness, vulnerability, and fear of the pandemic, which may increase anxious and depressive symptoms and negatively impact the quality of sleep. In another study, the reduction in sleep quality during lockdown was related with sleep reduction, going to bed later, getting up earlier, reduced exposure to daylight and increased screen use in the evening [68]. Recently Raman et al. [70] demonstrated that social jetlag does not mediate the relationship between chronotype and sleep quality: later

MSFsc was weakly associated with poorer sleep quality and greater social jetlag was weakly associated with poorer sleep quality, except in males.

Chronotype: Synchrony effect and circadian disruption on basic and complex cognitive functions

Most cognitive components show homeostatic and circadian variations. Moreover, under the influence of the sleep-wake regulation, cognitive functions fluctuate throughout the day with optimal performance occurring at different times. The “synchrony effect” is considered to be the difference in performance between the optimal and suboptimal times of day according to chronotype [71]. Since chronotype is associated with optimal timing of daily performance on cognitive tasks, a “synchrony effect” occurs between chronotype and time of testing (i.e., evening types perform better later in the day, morning types earlier in the day, and reciprocally) [71, 72]. However, the impact of sleep and circadian disruption on neurocognitive performance such as attention and memory, and on higher-order executive functions such as response inhibition and decision-making, remains unclear [73-78].

Sleep deprivation is known to affect alertness [79, 80]. Circadian variability differentially affects alertness at different times of the day. Morning types tested in the morning and evening types tested in the evening respond faster on tasks measuring their reaction time (RT), such as the Psychomotor Vigilance Task [81]. Vigilant attention is activated when rather monotonous tasks are performed over long periods of time. While studies have found chronotype and time-of-day interactions (i.e., synchrony effect) on tasks requiring vigilant attention (e.g., the PVT) [82, 83], others have not evidenced this synchrony effect [43].

Interestingly, the performance of morning types has been shown to be less impacted by suboptimal times than that of evening types, who manage to maintain more stable

performance over longer periods of time regardless of the time of day [84]. Attention-dependent conflict-resolution on demanding cognitive tasks does not seem to be modulated by chronotype or time of testing [84].

Attention components show homeostatic and circadian variations in alertness as well as in selective attention and sustained attention [85]. Attention improves during the day with higher levels during the afternoon and evening hours, while lowest levels are observed during nighttime and early in the morning. Importantly, the circadian rhythm in attention during the night and early morning hours is associated with an increased risk of errors and accidents [86]. However, this time course may depend on chronotype, sleep deprivation and/or age [85, 87-90]. Indeed, age-related changes occur in the homeostatic and/or circadian aspects of sleep regulation, i.e. an attenuation of the circadian influence on cognitive processes and a reduction in sleep pressure with duration of time awake [87, 89, 91]. Curiously, however, it remains unclear why the characteristics of attentional tasks such as novelty and cognitive demands may compensate for the low level of alertness at non-optimal times of the day in morning types [84]. Several studies have highlighted the importance of sleep in memory [92]. A time-of-day effect in the prospective memory of young adults has been shown by their better performance in the evening hours, irrespective of their chronotype [74].

Sleep deprivation seems particularly to impair complex executive functions involving the prefrontal regions [91, 93, 94]. However, some studies failed to demonstrate such effects [95-97]. These inconsistencies may be attributable to inter-individual differences or to activation of mechanisms in the prefrontal cortex that compensate for sleep deprivation [73]. Higher-order cognitive functions and cognitive control including inhibitory control are influenced by circadian phase and homeostatic sleep drive [98]. Regarding the influences of

sleep pressure on executive performance, a study found that inhibitory motor control (i.e., ability to inhibit an inappropriate response) and sustained attention (i.e. ability to respond accurately to appropriate stimuli) on an executive task (i.e., go/no task) are decreased by extended wakefulness at all ages [91]. Regarding the influence of the circadian system, the authors found that error-related processing (i.e., commission and omission errors) on a behavioral inhibition task did not seem to be regulated by circadian processes, unlike speed-related processing (i.e., reaction times).

Executive function and neurocognitive performance are intrinsically circadian in their organization and are therefore particularly susceptible to disruption [72]. Synchrony effects are also expected on cognitive demanding tasks requiring sustained attention to maintain an accurate level of performance, such as those involving attentional control (e.g., Stroop or Flanker interference tasks) or inhibitory control [83]. A synchrony effect was replicated in tasks demanding cognitive control such as executive control [99] and response inhibition [71, 72]. Subsequent research suggests that controlled processes could be more sensitive to the synchrony effect than automatic processes [83].

Social jetlag is associated with greater impulsivity and inattention [100] and impaired reward-related brain function [101]. A recent cross-sectional study on healthy young adults [78] showed that it may impact attentional/inhibitory performance, as more impulsive responding as evidenced by faster and less variable reaction times and increased commission errors on a response inhibition task. The study also found that chronotype did not impact attentional/inhibitory performance [78]. However, individual differences in inhibition-related cerebral activation after sleep deprivation seem to be influenced by chronotype [75].

The effects of circadian synchrony on decision-making remain unclear [77]. Risky behavior increases with sleep deprivation [102]. Eveningness is associated with self-reports of high impulsivity, risk-taking propensities, novelty and sensation-seeking [103]. However, this association does not translate easily from the subjective to the behavioral level when subjects are faced with risk-taking tasks that have real outcomes or consequences. A study found that decision-making depended on individual differences in circadian rhythmicity rather than on time of day [77]. However, in a recent study, the time-of-day effect was found to regulate risky decision-making and inhibitory control [104]. Individuals were found to act with higher risk preference, less sensitivity to loss as negative feedback, and lower inhibitory control in the afternoon than in the morning [104]. The authors concluded that the effects of time of day on risk propensity and inhibitory control are relatively independent.

Unlike subjective poor sleep quality [78, 102] or sleep loss [105], neither chronotype nor social jetlag were found to be associated with risky decision-making [78]. However, the circadian cycle may impact higher-order cognitive functions [98] and chronotype may exert a greater influence on performance at non-optimal moments of the day [71].

Evening types are less able to adapt to suboptimal times than morning types, because they have to deal with social jetlag and decreased self-control [106]. Therefore, morning types may have better cognitive and academic performance thanks to the better alignment of their internal clock (circadian rhythm) and because academic activities usually start early in the morning [107]. Moreover, social jetlag may be more detrimental to academic performance in adolescent girls, since the shift to eveningness occurs earlier in girls due to their earlier pubertal development [108].

To conclude, the effects of sleep deprivation and time of day appear to differ across cognitive domains according to chronotype. Evening types may show vulnerabilities in cognition that are reinforced by social jetlag, but they may also display increased inhibition-related cerebral activation as a compensatory response after sleep deprivation. However, the lack of consensus could be due to differences in task characteristics, dependent variables, study population, and experimental design. For example, participants may be instructed to follow a fixed sleep-wake schedule instead of their own preferential sleep schedules [43]. Future multidisciplinary research involving psychology, physiology, chronobiology and cognitive neuroscience domains could focus on individual differences in cognitive processes after sleep deprivation, circadian disruption and social jetlag. Their interactions should be explored with a consensus methodology that considers the individual time plans of the participants to control circadian and homeostatic processes.

Chronotype: relationship with depression or with attention deficit hyperactivity disorder (ADHD)

The enthusiasm for the investigation of chronotype or morningness-eveningness in the context of mental disorders has grown in the last 20 years. It is now acknowledged that chronotype and/or social jetlag can influence physical and mental health [39]. The increased prevalence of eveningness in various disorders such as mood disorders, substance abuse, sleep disorders and ADHD has been well established [109, 110]. To illustrate these links, this section focuses on the links between chronotype, on the one hand, and depression and ADHD, on the other.

We already confirmed the relationship between depression and eveningness (assessed by self-reported morbidity questionnaire) in a population of 1165 non-shift workers with an

average age of 50 years [51]. This relationship appears from an early age. For example, in children aged 7 to 13 years, a higher tendency to depression was associated with eveningness [111]. Among adolescents, evening-types exhibit later depression and adolescents with a history of earlier depression exhibit eveningness [112]. Moreover, the relationship between internalizing symptoms and chronotype is specific to depression [113]. Eveningness appears to be a risk factor for depressive symptoms and the onset of a depressive disorder among young people [109].

The relationship between eveningness and depression and its symptoms was confirmed by the recent work of Bauducco et al. [114], who reviewed articles published in the previous two years (2017-2019) (N=133348, mainly adolescents). In adults, the recent meta-analysis (data from 36 studies; n =15734) by Au et al. [110] confirmed these links and demonstrated a difference in chronotype between depressed and non-depressed individuals. They found that an individual's chronotype is related to their depressive symptomatology, eveningness being significantly associated with more severe symptoms. Mood depressive disorders appeared to be more evening-oriented than other depressive disorders. Furthermore, subgroup analyses revealed that age and gender did not moderate the relationship between morningness-eveningness and depressive symptomatology.

Various hypotheses have been proposed to explain how circadian dysfunctions could contribute to the pathophysiology of depression. One of them suggests that genetic vulnerabilities, such as mutations in specific clock genes, could induce changes in the intrinsic period and phase angle of entrainment [115]. This circadian disruption may modify the rhythmic activity of the neurotransmitter systems involved in mood regulation, including dopamine and serotonin [116], leading to a preference for eveningness and the development of depressive symptoms. Another hypothesis is that insomnia symptoms

facilitate the onset of mood disorders and exacerbate their severity [117]. Comorbidity between insomnia and depression is frequent with up to 40.5% of depressed patients meeting the diagnostic criteria for insomnia [118]. Circadian abnormalities, particularly delayed rhythms, may also play a role in the pathogenesis of depressive disorders [115]. Circadian and sleep disruptions in depressed patients have been linked to abnormal clock gene expression [119] and might explain why depressive symptoms occur more in evening-types [38]. In a systematic review, Henderson [120] demonstrated that social jetlag is associated with clinical depression, especially with seasonal depression, only in female living in high latitude regions.

This association between late chronotype and depression could have clinical implications and could improve the prevention, diagnosis and treatment of mood disorders. A major issue is to recognize the factors associated with depression and to identify subjects who may be vulnerable. Morningness-eveningness may be used as a tool for identifying individuals at risk of developing mood disorders, particularly during adolescence before the onset of mood symptoms [121].

Attention deficit hyperactivity disorder (ADHD) is the most common developmental disorder and is characterized by inappropriate levels of inattention, impulsivity and hyperactivity. These symptoms must have been persistent for more than 6 months with negative social, academic, and/or occupational consequences [122]. The prevalence of ADHD is estimated at 5% in children and adolescents [122]. Follow-up studies have documented the persistence of ADHD into adulthood in 50 to 65 % of cases [123]. Sleep disorders have been extensively investigated in individuals with ADHD and their prevalence is reported to be in the range 25-55% [124, 125]. Chronic sleep insomnia is one of the most common sleep disorders in

children and adults with ADHD [126, 127]. Given this high prevalence of insomnia in ADHD, recent attention has begun to focus on the role played by circadian disruption.

In their first review on this topic, Snitselaar et al. [128] concluded that ADHD in adults is associated with delayed circadian rhythmicity and with a delayed sleep phase disorder.

Coogan and McGowan in their recent systematic review [129] confirmed these findings and showed that ADHD is associated with late chronotype and with delayed circadian phase.

While more than 40% of adults with ADHD display eveningness, only about 11% of age-matched healthy peers did [130]. Delayed sleep circadian phase may be linked to the sleep onset insomnia and the delayed sleep phase disorder observed in ADHD patients. Similarly, a recent study [131] investigated the prevalence of delayed sleep phase disorder (DSPD) in patients with ADHD. As expected, comorbidity was common with 33% of the subjects classified in the combined group ADHD and DSPD. Moreover, more patients in the sub-group with DSPD presented eveningness. The combined diagnosis has an impact on global functioning, which underlines the importance of diagnosing and treating this specific phenotype.

Because adolescence is a developmental period characterized by disruptions in sleep and changes in circadian preference, adolescents with ADHD require special attention. Becker SP et al. [132] examined circadian preference in ADHD patients and its impact on sleep and daytime functioning. Greater eveningness was associated with both sleep problems and daytime sleepiness, as assessed by adolescents and their parents. Another key issue is the link with obesity. Children and adolescents with ADHD have a high prevalence of obesity [133], although the relationship between these two problems is not clear. Research on eating behaviors and circadian preferences has shown that individuals with the evening chronotype have worse control over feeding than those with the morning chronotype [134].

One hypothesis is that sleep problems and hyperactivity/impulsivity appear to mediate the relationship between chronotype preference and feeding. Eveningness may be a component linking ADHD symptoms to overweight/obesity [135, 136]. Fueling this hypothesis, the work conducted by Turkoglu [137] demonstrated that evening preference was directly related to obesity, while morning preference was directly related to normal weight. Moreover, ADHD index, which is an overall indicator of the severity of ADHD, was related to BMI. These results may explain why the sub-group of patients with ADHD and obesity did not respond well to standard treatment for obesity. It is therefore important not only to treat obesity but also propose specific therapeutic strategies that target overweight, ADHD and sleep/wake cycles. In adults, social jet lag is a significant predictor of ADHD symptoms [100] but Langberg [138] demonstrated that in adolescents with ADHD or without ADHD, ADHD status was not associated with social jetlag.

Several hypotheses have attempted to explain the link between ADHD and circadian dysfunctions. Some genetic studies point to polymorphisms that link circadian clock genes with ADHD [139, 140], indicating a possible genetic overlap that could contribute to circadian dysfunctions. The analysis of rhythmic clock gene expression in patients with ADHD has shown circadian abnormalities at the molecular and behavioral level [141]. The review by Coogan [129] found only a small number of genetic association studies that reveal linkages between polymorphisms in circadian CLOCK genes (C/T SNP in the 3'-untranslated region of CLOCK rs1801260 with T allele conferring risk) and ADHD symptoms. An SNP in PER3 has recently been linked with ADHD in adults [142]. On the other hand, GWAS studies did not confirm the association between clock gene polymorphism and ADHD [143]. This non-association is discussed by Korman [144] who posit that clock gene polymorphisms do not confer an increased stand-alone genetic risk for ADHD diagnosis, but may confer an

increased risk for ADHD symptom severity in interaction with environmental factors. Dim light melatonin onset (DLMO) may also be implicated in the pathophysiology of ADHD with delayed sleep phase syndrome (DSPS). DSPS is also accompanied by delayed biomarkers of circadian function (DLMO, delayed cortisol rhythms, delayed sleep timing and delayed core body temperature rhythms [70]). Subjects with DSPS have phase-delayed DLMO, which is thought to contribute to their delay in sleepiness and sleep [145]. For example, in the study by Bijlenga et al. [146], DLMO was about 1.5 hours in the ADHD adult group compared to matched healthy controls. Raman [70] posited that impulsivity, which is a symptom of ADHD, increases temporal discounting and bedtime resistance, which in turn promotes nocturnal activities that then delay the circadian clock via exposure to light in the evening.

If ADHD patients present circadian abnormalities, there is an impact in terms of therapeutic strategies. For example, treatment for an ADHD patient with DSPD should combine psychoeducation, sleep hygiene, morning bright light therapy and the administration of low-dose melatonin in the evening [147]. In this context, melatonin is usually utilized as a somnolent and not as a chronobiotic, whose key effect would be to advance the circadian phase. Van Andel [148] recently showed that low doses of melatonin advanced the circadian rhythm and reduced self-reported ADHD symptoms in adults with ADHD. Treating delayed sleep with melatonin is an important component of effective ADHD treatment. Moreover, stimulant and non-stimulant medications may also impact sleep. Stimulants have also proved beneficial for treating insomnia in some ADHD patients [149], although data on the impact of ADHD medication on circadian function remain sparse.

Conclusion

Individual differences in sleep timing depend on the intrinsic period, the amplitude of circadian drive, the kinetic of homeostatic drive, and the phase angle of entrainment. Age (adolescence) and gender (male) as well as environmental light levels explain a substantial proportion of variation in chronotype. Genetic variation is also an important contributor to chronotype [59]. Individual differences in sleep timing may be assessed in two ways: either with a questionnaire like the MEQ, which classifies people into types according to what time they choose or prefer to sleep and to perform activities had they the opportunity to do so; or with a questionnaire like the MCTQ, which assesses chronotype by calculating a proxy of the phase angle of entrainment on free days. Generally, a quarter of the general population are extreme types or chronotypes and the rest are intermediates. During adolescence, the evening type or late chronotype is the most common. With age, the variability in chronotype decreases and only early chronotypes or morning types remain, whatever the questionnaire used. However, **if MEQ scores are interpreted differently, a quarter of subjects over 45 years of age may be considered as extreme types and the rest as intermediates** [36]. Some authors claim that chronotype is a stable personal trait, others that it is a “biological construct”. Notwithstanding this controversy, all studies confirm that the social time of late chronotypes during weekdays is not adapted to their internal circadian time because they are out of phase with it, unlike on free days when they come back into phase. This results in social jetlag and circadian disruption, which in turn leads to a chronic sleep debt due to a late spontaneous bedtime and an early induced wake time, which is then compensated on free days. Nocturnal artificial light and the proliferation of the new technologies and social media have led to both chronotypes going to bed even later, especially adolescents. For this reason, morning types run the risk of developing a sleep debt on workdays that they cannot completely offset on free days. In addition, social jet lag induces a “wake effort” period after

wake time. Sleep and circadian clock disruption generally alter cognitive performance (alertness, attention, memory, higher-order executive functions such as response inhibition and decision making) but their impact remains to be clarified. When subjects adopt their preferred sleep timing, a “synchrony effect” often appears with chronotype performing better during daytime at optimal than at suboptimal timing (late chronotypes perform better in evening time, early chronotypes in morning). Evening types appear to be cognitively more vulnerable to suboptimal times than morning types, probably because having to deal with social jetlag. Social jetlag increases impulsivity and inattention and may hamper decision-making. Social jetlag may be seen as a transitory “state” or a “sleep behavior” that can vary from one day to another or from one week to another, especially among evening subjects who demonstrate greater intraindividual variability in sleep timing. An effective countermeasure to decrease social jetlag is to reduce one’s exposure to evening light [31, 150]. Delaying social cues such as the moment work or school begins leads to an initial reduction in social jetlag [151], but this is only transitory [31]. Roenneberg et al. [27] draw attention to a common misconception about social jetlag, i.e. that the problem stems from sleeping too long at weekends. The popular press and some sleep specialists may go as far as telling people to get up at the same time at weekends as they do during their working week. Although sleep extension during week end so is probably not sufficient to offset one’s sleep debt and induce a circadian delay it nonetheless seems to prevent the harmful effects of chronic sleep deprivation on health and mortality [152]. There is also a large body of evidence demonstrating an association between chronotype and/or social jetlag, on the one hand, and mood disorders or ADHD, on the other. Since the reduction in social jetlag during lockdown for COVID-19 appears to have had little effect on mood disorders [67] or ADHD [153] and because light therapy may be proposed as a first-line treatment for seasonal and

non-seasonal depression [154], we suggest that morningness-eveningness rather than social jetlag may be used as a tool for identifying individuals at risk of developing mood disorders or ADHD, particularly during adolescence before the onset of mood symptoms.

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Figure captions

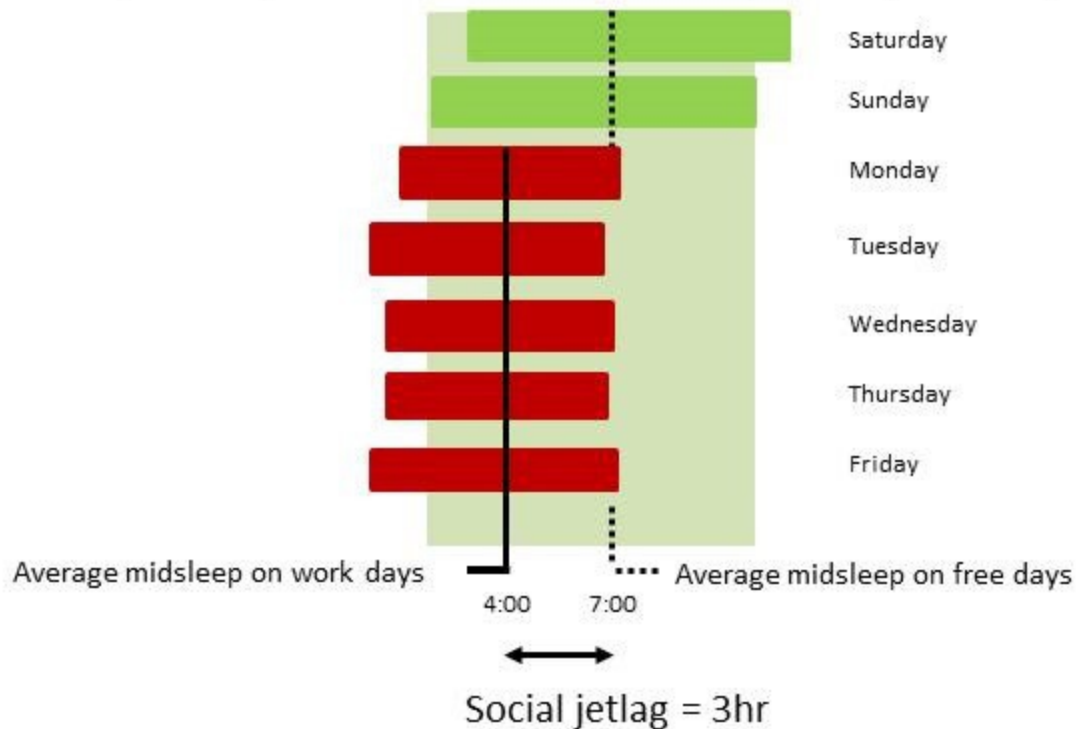
Abstract figure : Circadian (C) and homeostatic (H) regulation of sleep timing inspired by [1] and [23] and modification of strength of external factors (arrow thickness) responsible for the circadian misalignment and consequences.

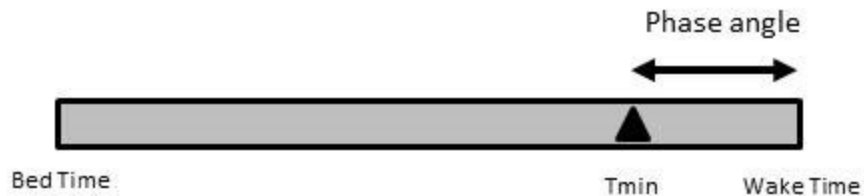
Figure 1: Example of social Jetlag. The green area represents the circadian sleep windows and sleep timing. Green bars represent sleep timing on free days (proxy for circadian time) and red bars represent sleep timing on work days (proxy of social time). The black vertical lines represent the midpoint of sleep on workdays (MSW) and on freedays (MSF, used to estimate chronotype). The difference between MSW and MSF is used to compute social jetlag.

Figure 2: Up: representation of the phase angle between wake time and circadian rhythm of core body temperature (represented by temperature minimum, T_{min}). Down: phase angle of entrainment in longer or shorted intrinsic periods of circadian clock, in morning- or evening-types and in subjects with or without of social jetlag. When phase angle is short, subjects wake up at a later local time but wake up at an earlier circadian time.

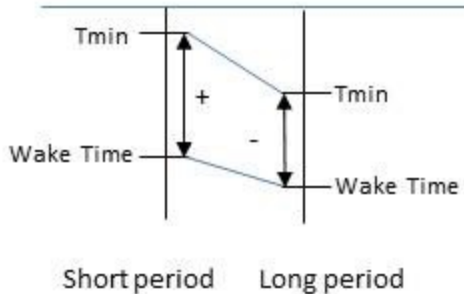
Figure 3: Major factors influencing homeostatic and circadian regulation of sleep timing resulting in differences in intrinsic circadian period, circadian phase entrainment and kinetic of sleep pressure leading in to different chronotypes (morning lark or evening owl)

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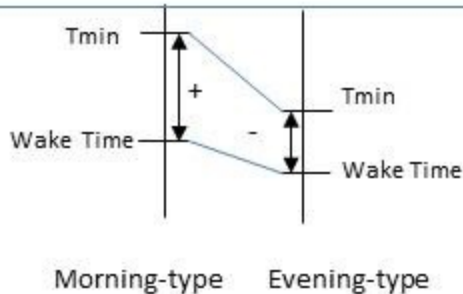




Intrinsic circadian period



Chronotype



Social jetlag

