University of Groningen

Conflicted clocks: Social jetlag, entrainment and the role of chronotype

Zerbini, Giulia

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Zerbini, G. (2017). *Conflicted clocks: Social jetlag, entrainment and the role of chronotype: From physiology to academic performance; from students to working adults*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 17-05-2025

Chapter 1

General introduction

Giulia Zerbini

Clocks everywhere, but what time is it?

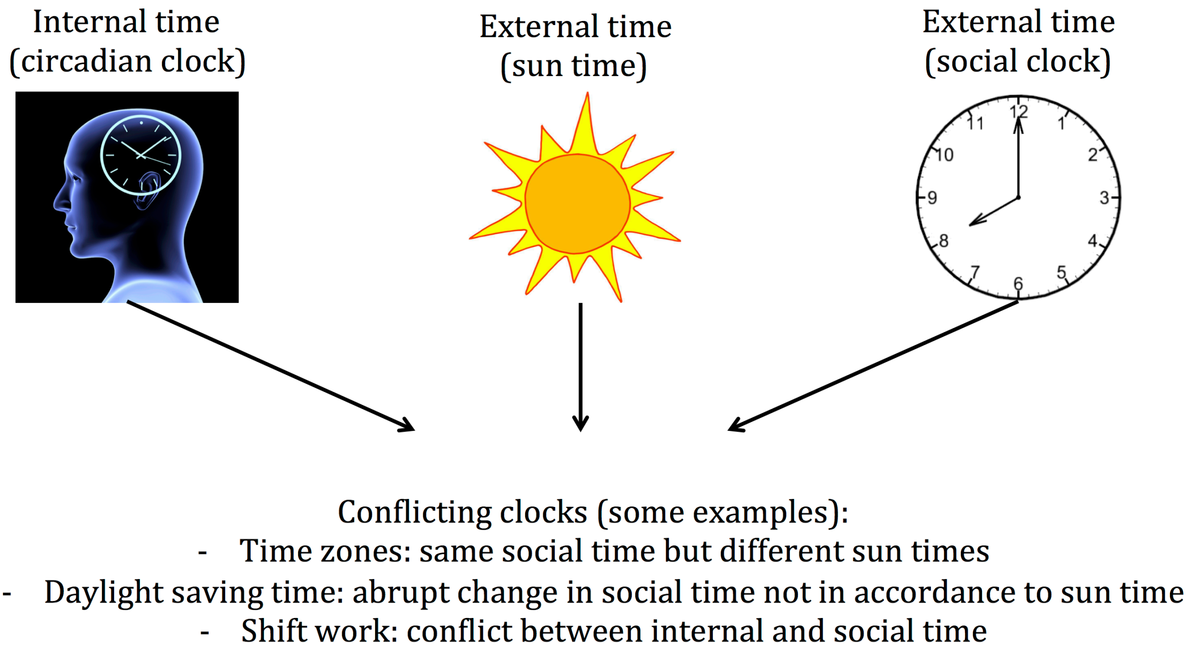
The rotation of the earth on its axis and around the sun determines regular changes in the environment, namely the alternation of day and night and of seasons. Many organisms have developed an internal time keeping mechanism in order to synchronize to external time signals (zeitgebers). The process that maintains a stable phase relationship between two oscillators is called entrainment (Aschoff, Klotter, & Wever, 1964). Having an internal clock able to entrain is thought to be adaptive since it allows, for example, anticipation of the regular changes in the environment (Moore-Ede, 1986). Light is considered the most important zeitgeber for human entrainment (Duffy & Wright, 2005; Roenneberg & Foster, 1997; Roenneberg, Kumar, & Merrow, 2007b; Skene, Lockley, Thapan, & Arendt, 1999; K. P. Wright et al., 2013). The internal clock has a period of about 24 hours (similar to the period of its zeitgeber) and is hence also called circadian clock (from Latin: circa diem = about a day).

In addition to light, there are several other zeitgebers that influence entrainment. For instance, food and physical activity have been shown to be able to entrain the behavior of animals even in the absence of light (Marchant & Mistlberger, 1996; Stephan, Swann, & Sisk, 1979). Non-photic entrainment has been described also in humans, although non-photic zeitgebers (e.g. physical activity, sleep-wake cycle, meal timing, social contacts) are much weaker time signals than is light (Mistlberger & Skene, 2005). Entrainment is therefore a complex phenomenon that can be challenged when the different time signals (external and internal) are not perfectly synchronized (Fig.1). For instance, different areas within a time zone have the same local clock time but different sun times (e.g. dawn in the eastern part of a time zone occurs earlier than in the western part of the same time zone). Similarly, daylight saving time shifts the social clock back and forth by 1 hour in spring and autumn, while sunset and sunrise times change gradually across the seasons. Shift-work is another example of how the social clock demands some individuals to be active at night when the circadian clock (in accordance to sun time) would promote sleep.

The main objectives of this thesis were to describe the negative consequences that can rise from conflicting internal and external time signals (part 1; chapters 2-5), to explore possible solutions to reduce the mismatch between the circadian and social clocks (part 2; chapter 6), and to better understand entrainment in real life conditions (part 3; chapters 7 and 8).

Variability in internal time

On top of the incongruences between different external time signals, internal time can vary substantially between individuals. Like many biological traits, also circadian clocks vary with individual characteristics such as sex, age, and genetic background (Hamet & Tremblay, 2006; Roenneberg, Kuehnle, Juda, Kantermann, et al., 2007a; Roenneberg et al., 2004). The additional exposure to different light landscapes results into a wide distribution of phases of entrainment, which determines, for instance, differences in sleep timing (Roenneberg & Merrow, 2007). These individual differences have been described as a distribution of chronotypes (Roenneberg, Kuehnle, Juda, Kantermann, et al., 2007a).



Conflicting clocks (some examples):

- Time zones: same social time but different sun times
- Daylight saving time: abrupt change in social time not in accordance to sun time
- Shift work: conflict between internal and social time

Figure 1. Internal time, sun time, and social time.
Internal and external time signals are not always perfectly synchronized in modern society, giving rise to several conflicts. Some examples of these conflicts are listed.

Chronotype and how to measure it

Chronotype is a feature of the circadian clock that can be easily measured via questionnaires such as the Munich ChronoType Questionnaire (MCTQ; Roenneberg, Wirz-Justice, & Merrow, 2003) and the Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976). Chronotype assessed via the MCTQ refers to sleep timing on work-free days, while the MEQ expresses chronotype as a diurnal preference towards morningness or eveningness. The answers to these questionnaires are highly correlated (r = -0.73) and show a variety of chronotypes ranging from very early (morning) to very late (evening) types (Zavada, Gordijn, & Beersma, 2005). In our studies, we use the MCTQ because expressing chronotype as a clock time gives more insight on the interaction between internal and external time.

With the MCTQ, chronotype is assessed as the midpoint of sleep on work-free days (MSF). For example, if one sleeps from 00:00 h to 08:00 h, MSF is 4. The majority of the working population (80%) needs alarm clocks to wake up on workdays (Roenneberg, Kantermann, Juda, Vetter, & Allebrandt, 2013); hence most people are chronically sleep deprived, showing sleep rebounds on work-free days to compensate for the lost sleep. Because of this tendency to oversleep on work-free days, MSF has to be corrected for the confounding influence of sleep debt accumulated on workdays, resulting in MSF sleep corrected (MSF_{sc}). This difference in sleep duration between workdays and work-free days is particularly evident in late chronotypes (if they have to attend early school/working schedules). Generally, the later the chronotype, the shorter the sleep duration on workdays and the longer the sleep duration on work-free days will be (Roenneberg, Kuehnle, Juda, Kantermann, et al., 2007a).

Characteristics of chronotype

Chronotype varies with age and sex. The prevalence of morning types is higher in the toddler age, but a progressive delay in chronotype is clear already during the first years of age (Randler, Faßl, & Kalb, 2017). Males on average are later than females, and this becomes particularly evident during adolescence (Randler et al., 2017; Roenneberg et al., 2004; Roenneberg, Kuehnle, Juda, Kantermann, et al., 2007a). Based on the MCTQ database, males reach their maximum in lateness at the age of 21, whereas females, who mature earlier, reach their maximum in lateness at the age of 19.5. After that age, both gradually become earlier chronotypes. When using another questionnaire to assess chronotype as diurnal preference (Composite Score of Morningness; Smith, Reilly, & Midkiff, 1989), these peaks in lateness are observed earlier (at the age of 18 for males and at the age of 15 for females; Randler et al., 2017).

Chronotype varies also with light exposure as shown by the correlation between chronotype and time of dawn described in a German population (Roenneberg, Kumar, & Merrow, 2007b). Moving from east to west, dawn was shown to progress continuously and the same was true for chronotype that was found to delay from east to west, although local clock time was the same within the given time zone. The correlation was stronger for smaller towns (less than 300,000 inhabitants), where people hypothetically experience a stronger zeitgeber since they spend more time outdoors and are exposed to more natural light than people living in bigger cities. This finding suggests the importance of considering sun time as well as total outside light exposure since the circadian clock seems to entrain to natural light rather than social schedules.

Genetic influences on chronotype have been also described in relation to extreme sleep behaviors, such as advanced and delayed sleep phase syndromes (Archer et al., 2003; Hamet & Tremblay, 2006).

Chronotype and other tools to assess phase of entrainment and sleep timing

Chronotype can be used to estimate an individual's phase of entrainment. Although chronotype is assessed with questionnaires (subjective measurement), the MCTQ asks about sleep timing that is usually reported quite objectively. The greatest advantage of using chronotype to assess phase of entrainment is the possibility to collect data in large populations in a quick and cost-effective way; the MCTQ online database has in fact reached over 200,000 entries so far.

Alternatively, biological (objective) phase markers can be used in human research to determine phase of entrainment, especially in relatively small-sample-size studies. Dim-light melatonin onset (DLMO) is often the first choice because melatonin has a robust and stable rhythm under the direct control of the circadian clock (Arendt, 2006; Klerman, Gershengorn, Duffy, & Kronauer, 2002). Melatonin is suppressed by light and therefore needs to be assessed in dim-light conditions. Other markers of the melatonin rhythm can be used, such as the peak in expression, but the advantage of DLMO is that it is accepted as a proxy for a full, overnight melatonin curve in most experiments (less expensive and time consuming). Importantly, chronotype, both assessed with the MCTQ and the MEQ, is generally strongly correlated with DLMO (MCTQ: $r = 0.68$; MEQ: $r = -0.70$; Kantermann, Sung, & Burgess, 2015).

Another biological phase marker mainly used in laboratory studies is core body temperature. Core body temperature also shows a strong circadian rhythm with a peak in the evening and a trough at night, but is more variable and influenced by external factors such as physical activity more than is melatonin (Klerman et al., 2002).

Sleep timing can be assessed both with daily sleep diaries (subjective measurement) and with actiwatches (objective measurement) that usually record activity together with light exposure. Actigraphy data can give also insights about sleep quality based, for instance, on awakenings and the time spent asleep in relation to time spent in bed (sleep efficiency). Actigraphy can also be used to assess other phase markers such as center of gravity (the time point when the amount of activity before and after is the same).

Conflicting clocks: consequences and possible solutions

Although individual differences in sleep timing and diurnal preferences have been widely described, society often imposes the same (early) social schedules on everyone, independent of their chronotype. This has consequences in terms of performance and health. For instance, a synchrony effect has been shown in literature, whereby early chronotypes perform better in the morning and late chronotypes perform better in the afternoon when tested with different cognitive tasks (Goldstein, Hahn, Hasher, Wiprzycka, & Zelazo, 2007; Lara, Madrid, & Correa, 2014; May, Hasher, & Stoltzfus, 1993). Similarly, there is a growing body of literature about the influence of chronotype on school performance. Students are expected to be at school early in the morning (some schools start at 7:00 h), while their circadian clock is considerably delaying during puberty (Crowley et al., 2014; Randler et al., 2017; Roenneberg et al., 2004). It is quite common for adolescents to have a chronotype around the same time when schools start, meaning that they are taught and take examinations in the middle of their biological night. This results in late chronotypes usually obtaining lower grades compared to early chronotypes (Borisenkov, Perminova, & Kosova, 2010; Escribano, Díaz-Morales, Delgado, & Collado, 2012; Randler & Frech, 2009; van der Vinne et al., 2015; Vollmer, Pötsch, & Randler, 2013). The interaction between chronotype and other factors important for school performance is complex and is further addressed in chapter 5, a review article about our and previous findings on this topic.

Social jetlag and health issues

The mismatch between the circadian and social clocks can be quantified by assessing social jetlag. The term social jetlag was coined by the group of Till Roenneberg in 2006 (Wittmann, Dinich, Merrow, & Roenneberg, 2006). Social jetlag is assessed with the MCTQ as the absolute difference between the midpoint of sleep on workdays (MSW) and on work-free days (MSF). MSW is a phase marker for sleep timing driven by the social clock, and MSF is a phase marker for sleep timing driven by the circadian clock. Therefore, the absolute difference between MSW and MSF is a measure of the discrepancy between the circadian and social clocks. Since social schedules start generally early in the morning, late chronotypes are the ones who suffer from social jetlag the most (Wittmann et al., 2006).

Social jetlag has been found to be associated with several health issues. Social jetlag significantly increases the probability of overweight and is positively associated with weight gain within this specific sub population (Roenneberg, Allebrandt, Merrow, & Vetter, 2012). Furthermore, stimulant consumption is related to social jetlag and, in particular, the greater the social jetlag, the more likely someone is a smoker (Wittmann et al., 2006). A positive correlation between social jetlag and depressive symptoms has also been found in a rural population in Brazil (Levandovski et al., 2011). Social jetlag is particularly high in shift workers and is positively correlated with heart rate, considered as a marker for cardiovascular diseases (Kantermann et al., 2013). Given all these findings, we hypothesized that a decrease in social jetlag could be beneficial in terms of improved health and performance, especially for those who experience a considerable discrepancy (more than 2 hours) between their circadian and social clocks. Finding practical and effective ways to decrease social jetlag was the second main objective of this thesis. Since social jetlag arises from a discrepancy between two clocks, there are two possibilities to decrease it: delay the social clock or advance the circadian clock. Several schools and working places have introduced delayed or flexible schedules, but still there are many situations in which late chronotypes need to perform at an early (non-optimal) time of day. Therefore, more studies investigating interventions to decrease social jetlag by modifying (advancing) phase of entrainment are needed.

How light influences the circadian clock and its entrainment

As previously described, light is the most important zeitgeber for human entrainment (Duffy & Wright, 2005; Roenneberg & Foster, 1997; Roenneberg, Kumar, & Merrow, 2007b; Skene et al., 1999; K. P. Wright et al., 2013). There are several characteristics of light that influence entrainment: wavelength, intensity, duration, time of day, and light history.

Almost two decades ago, a new opsin (melanopsin) was discovered in retinal ganglion cells (Provencio, Jiang, De Grip, Hayes, & Rollag, 1998). Melanopsin has a peak sensitivity around 470 nm (blue light) and is specifically responsible for the non-image forming effects of light, such as entrainment of the circadian clock (Brainard et al., 2001). Several studies have shown that blue light has the strongest effect on the circadian clock. For instance, melatonin suppression is higher after exposure to blue light compared to other colors (Brainard et al., 2015; Santhi et al., 2011; Thapan, Arendt, & Skene, 2001; H. R. Wright & Lack, 2009).

Other studies investigated the role of light intensity. Very low light intensities (1.5 lux) can entrain the human circadian clock in controlled laboratory conditions, but if the period of the light-dark cycle deviates from 24 hours (23.5 hours and 24.6 hours), higher light intensities are needed to achieve entrainment (K. P. Wright, Hughes, Kronauer, Dijk, & Czeisler, 2001). The response to light, in terms of melatonin phase shift and melatonin suppression, occurs in a dose-dependent manner. A single low light intensity pulse of 6.5 hours (below 15 lux for melatonin phase shift and below 80 lux for melatonin suppression) was found to trigger minimal responses in the circadian system (Zeitzer, Dijk, Kronauer, Brown, & Czeisler, 2000). With increasing light intensities, both phase shifting effects and melatonin suppression increased, reaching saturation above 200 lux for melatonin suppression and above 500 lux for melatonin phase shift (Zeitzer et al., 2000).

As for light duration, circadian phase shifts can be obtained with different light pulse durations. St Hilaire and colleagues (2012) showed that one hour of a bright white light pulse was sufficient to induce a phase shift of 2 hours, although it represented only 15% of a 6.7 hours light pulse, which, in a previous study, was shown to elicit a maximal phase shift (3 hours) of the circadian pacemaker (Khalsa, Jewett, Cajochen, & Czeisler, 2003; St Hilaire et al., 2012). Phase shifts of the circadian system have been also shown after exposure to a sequence of intermittent light pulses (Gronfier, Wright, Kronauer, Jewett, & Czeisler, 2004).

Time of day of light exposure is also an important factor. Light can have both advancing and delaying effects on the circadian clock. The phase response curve (PRC) describes the relationship between time at which a light pulse is presented and the direction of circadian phase shifts. The circadian system is more sensitive to light at the beginning and at the end of the biological night. In the first case, a light pulse induces phase delays, whereas in the second case the same light pulse induces phase advances (Khalsa et al., 2003).

Finally, the amount and intensity of light exposure (prior light history) during the day was shown to influence the sensitivity of the circadian system. For example, when the exposure to a light source followed a period in darkness or in dim light conditions, stronger responses in terms of phase shifts and melatonin suppression were found compared to when the same light pulse was applied after bright light exposure (Hebert, Martin, Lee, & Eastman, 2002).

Concept of decreasing social jetlag with light

Based on this literature, we developed two protocols involving light interventions to decrease social jetlag by modifying phase of entrainment and sleep timing.

The first protocol involved an increased exposure to (natural) morning light by sleeping with bedroom curtains open, and the second protocol involved a reduced exposure to (blue) evening light by wearing blue-light-blocking glasses. In both cases, we aimed to test the effectiveness of interventions that could be easily implemented in everyday life, since there is a lack of field studies confirming what has been already shown in controlled laboratory conditions.

We hypothesized that both the increased exposure to morning light and the reduced exposure to evening light would advance phase of entrainment and sleep timing, leading to longer sleep duration on workdays and therefore to a reduction of the sleep debt accumulated. This, in turn, would translate to less oversleep on work-free days, leading to a decrease in social jetlag via a better alignment of the midpoint of sleep on workdays and on work-free days (Fig. 2).

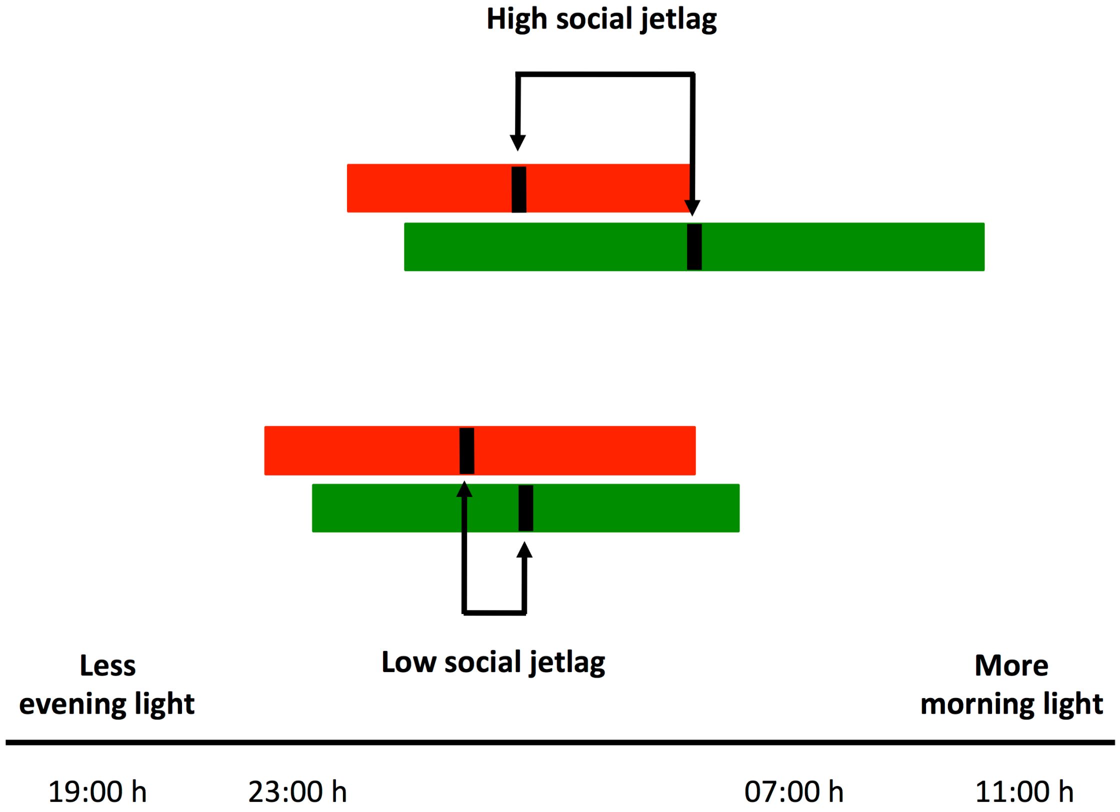


Figure 2. Decreasing social jetlag (SJL) with light.
The bars represent sleep duration on workdays (red) and on work-free days (green). The vertical black lines represent the midpoint of sleep on workdays (MSW) and on work-free days (MSF). SJL is the absolute difference between MSW and MSF. Light interventions involving less evening light and more morning light are both expected to advance sleep timing and phase of entrainment, leading to a longer sleep duration on workdays and therefore to a reduction of sleep debt accumulated. As a consequence, oversleep on work-free days is also expected to disappear. Altogether, this should result in a decrease of SJL via a better alignment of MSW and MSF.

Further understanding entrainment: the role of season and weekly schedule

Light is the primary zeitgeber for human behavioral entrainment, and therefore many studies have investigated the (isolated) effects of light on the circadian clock, often in highly controlled laboratory conditions. However, entrainment is a complex phenomenon resulting from the integration of many different internal and external time signals. Therefore, more field studies investigating entrainment in real life conditions may be useful to understand the problems and possibilities of giving sound advice to people who are not institutionalized.

At high latitudes, photoperiod (day length) varies substantially across seasons (e.g. in Amsterdam, The Netherlands (52° 22' N): summer photoperiod: 16:48 h and winter photoperiod: 7:40 h). This provides a unique opportunity to better understand entrainment in real life conditions by comparing, for instance, phase of entrainment between summer and winter. In summer, not only is photoperiod longer but also light intensity levels are generally higher. Increased light exposure was found to be associated to an earlier phase of entrainment, suggesting that phase of entrainment could be earlier in summer (Roenneberg & Merrow, 2007). Supporting this, sleep timing in humans was shown to track dawn by moving progressively to an earlier phase especially during the months of February and March when dawn comes minutes earlier each day (dawn on the 1st of February in Amsterdam: 8:21 h, dawn on the 31st of March 6:17 h) (Kantermann, Juda, Merrow, & Roenneberg, 2007).

It is important to note that in The Netherlands, like in many other countries in the world, daylight saving time (DST) is used during the summer months (April - October). During DST, social time is shifted one hour later. This was shown to disrupt entrainment and therefore might confound the findings from seasonal studies in humans (Kantermann et al., 2007).

The social clock also influences human behavior, in particular the sleep-wake cycle, but whether the social clock is able to change phase of entrainment is not clear yet. Sleep is usually later and longer on work-free days compared to workdays (social jetlag), and this difference is greater in later chronotypes (Wittmann et al., 2006). Because of the weekly schedule, workers are generally exposed to more morning light on workdays (Crowley, Molina, & Burgess, 2015). But is this difference in light exposure (only two work-free days a week) enough to phase shift the circadian clock every time over the weekend? It is possible that the sleep-wake cycle is quite flexible, but phase of entrainment remains stable.

Studies investigating the seasonal variation in the melatonin rhythm (as marker of phase of entrainment) have been inconclusive, probably because of the different conditions in which melatonin was assessed. Some have found no differences in DLMO, some an advance in melatonin peak in summer compared to winter, and some have found longer secretion of melatonin in winter compared to summer (Crowley et al., 2015; K. Honma, Honma, Kohsaka, & Fukuda, 1992; Illnerová, Zvolsky, & Vaněček, 1985; Stothard et al., 2017; Wehr, 1991).
Studies that have manipulated the sleep-wake cycle to simulate a typical weekend found a later DLMO associated with later and/or longer sleep (Burgess & Eastman, 2006; Crowley &

Carskadon, 2010; Jelínková-Vondrasová, Hájek, & Illnerová, 1999; Taylor, Wright, & Lack, 2008; Yang, Spielman, & Ambrosio, 2001). Therefore, the sleep-wake cycle seems able to feedback to the circadian clock and shift DLMO by probably changing the timing of light exposure between workdays and work-free days. However, whether this happens every week in a typical working population has not been shown yet.

Thesis overview

One of the main objectives of this thesis was to describe how conflicting internal and external clocks might result in negative consequences for human health and performance in order to suggest solutions. In particular, we focused on school performance in high-school students. We chose to study this population because chronotype delays during adolescence creating a conflict between the late circadian clocks of students and their early school schedules. In **chapters 2** and **3** we investigated the role of chronotype together with time of day (chapter 2) and school attendance (chapter 3) in determining school performance (grades). Previous literature had shown that late chronotypes obtain, on average, lower grades compared to early chronotypes. We expanded on this showing that the chronotype-effect on grades is complex, requiring a comprehensive assessment of the influence of chronotype together with other factors important for school performance, such as time of day and school attendance. In **chapter 4** we aimed to expand our previous results about the interaction effect between chronotype and time of day on grades. We chose university students as an interesting population because they are examined early in the morning as well as late in the evening. **Chapter 5** reviews the literature about chronotype and school performance with the aim of suggesting possible mechanisms behind a lower school performance in late chronotypes. Solutions to increase school performance in late chronotypes are also explored.

The second main objective of this thesis was to test the effectiveness of light interventions to decrease the mismatch between the circadian and social clocks (social jetlag). Light interventions were chosen for this purpose because light is the main zeitgeber for human entrainment and, if timed properly, it is capable of shifting (advancing) the circadian clock.
In **chapter 6** the findings from two studies are described. The light interventions implemented in these studies involved an increase in (natural) morning light exposure (by sleeping with bedroom curtains open) and a decrease in (blue) light evening exposure (by wearing blue-light-blocking glasses).

The final objective of this thesis was to better understand entrainment in real life conditions. We took advantage of the natural changes in photoperiod across seasons to assess how the variation in intensity and duration of light exposure might influence human behavior and entrainment. **Chapter 7** describes how school attendance and performance vary across seasons. Data were collected for two consecutive academic years. The role of photoperiod (day length) and of weather conditions was investigated in relation to the annual rhythm observed in school attendance. In **chapter 8** we investigated the influence of season (summer vs. winter) and weekly schedule (workdays vs. work-free days) on sleep timing, on phase of entrainment (DLMO), and on the relationship between these two parameters. The possible role of chronotype in influencing these variables was also investigated.

Finally, **chapter 9** summarizes the main findings of this thesis: the influence of chronotype on school performance and the effects of different light interventions and season on social jetlag, sleep timing, and phase of entrainment. The chapter integrates and connects these findings. The discussion focuses on late chronotypes, describing the challenges offered by early social schedules, the consequences in terms of impaired performance, and the possible solutions to decrease the mismatch between the circadian and the social clocks. In Figure 3 a schematic overview of this thesis is represented.

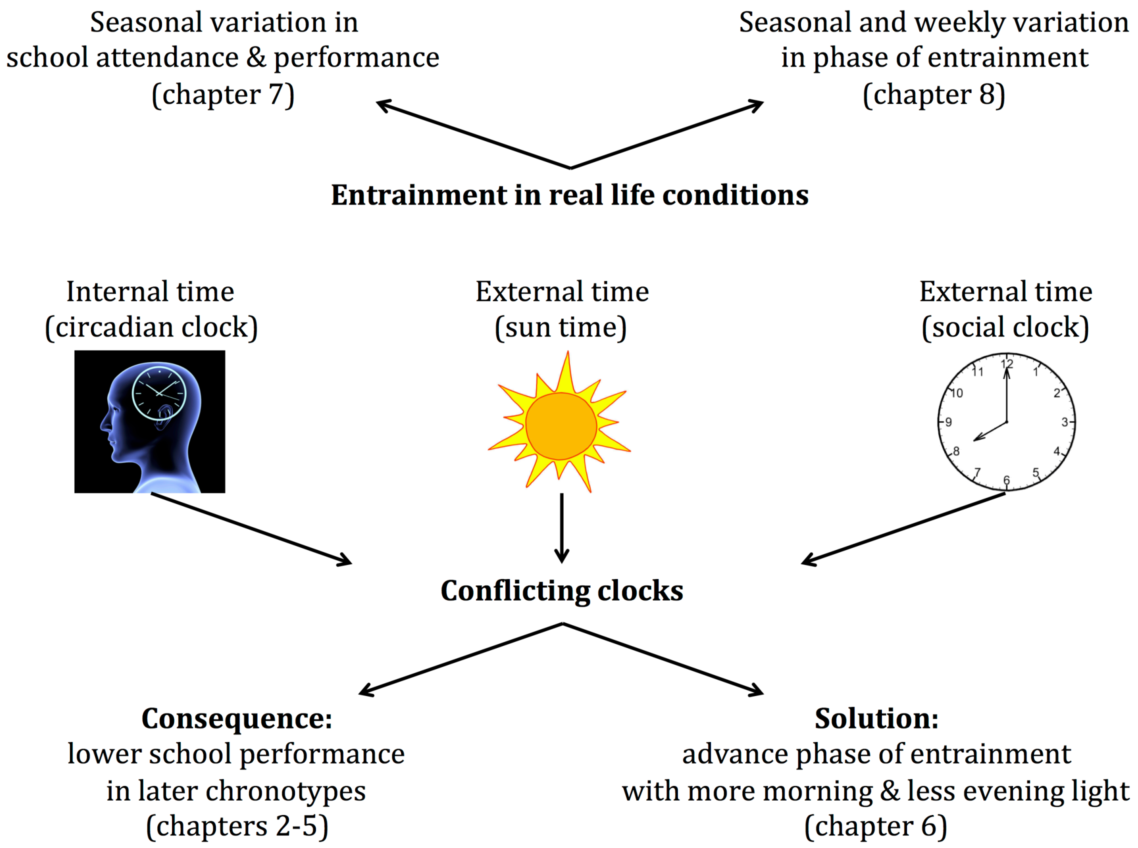


Figure 3. Schematic thesis overview.