Light and the Human Circadian Clock

Till Roenneberg, Thomas Kantermann, Myriam Juda, Céline Vetter, and Karla V. Allebrandt

Abstract The circadian clock can only reliably fulfil its function if it is stably entrained. Most clocks use the light–dark cycle as environmental signal (zeitgeber) for this active synchronisation. How we think about clock function and entrainment has been strongly influenced by the early concepts of the field's pioneers, and the astonishing finding that circadian rhythms continue a self-sustained oscillation in constant conditions has become central to our understanding of entrainment.

Here, we argue that we have to rethink these initial circadian dogmas to fully understand the circadian programme and how it entrains. Light is also the prominent zeitgeber for the human clock, as has been shown experimentally in the laboratory and in large-scale epidemiological studies in real life, and we hypothesise that social zeitgebers act through light entrainment via behavioural feedback loops (zeitnehmer). We show that human entrainment can be investigated in detail outside of the laboratory, by using the many 'experimental' conditions provided by the real world, such as daylight savings time, the 'forced synchrony' imposed by the introduction of time zones, or the fact that humans increasingly create their own light environment. The conditions of human entrainment have changed drastically over the past 100 years and have led to an increasing discrepancy between biological and social time (social jetlag). The increasing evidence that social jetlag has detrimental consequences for health suggests that shift-work is only an extreme

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T. Roenneberg (✉) • C. Vetter • K.V. Allebrandt
Institute for Medical Psychology, Centre for Chronobiology, Medical Faculty,
Ludwig-Maximilians-University, Goethestrasse 31, 80336 Munich, Germany
e-mail: till.roenneberg@med.uni-muenchen.de

T. Kantermann
Chronobiology - Centre for Behaviour and Neurosciences, University of Groningen,
Nijenborgh 7 9747 Groningen, The Netherlands

M. Juda
Department of Psychology, University of British Columbia, 2136 West Mall, V6T 1Z4,
Vancouver, BC, Canada

A. Kramer and M. Merrow (eds.), *Circadian Clocks*, Handbook of Experimental Pharmacology 217, DOI 10.1007/978-3-642-25950-0_13,

form of circadian misalignment, and that the majority of the population in the industrialised world suffers from a similarly ‘forced synchrony’.

Keywords Chronotype • Entrainment • Sleep • Zeitgeber • Zeitnehmer • Free-running period • Clock evolution

1 Introduction

Chronobiology investigates temporal structures, rather than the linear passing of time. The German language discriminates between linear time (*Zeit*) and temporal structures (*Zeitraum*; German for ‘time-space’; plural *Zeiträume*). Life on Earth is influenced by four *Zeiträume*, the tides (12.5 h), the day (24 h), the lunar month (28.5 days) and the year (365.25 days). One or more of these are represented by endogenous clocks in most organisms. Here we focus on the human circadian clock, specifically on the importance of light for the process that actively synchronises its endogenous day to that of the environment (entrainment).

Circadian clocks create an internal representation of the external *Zeitraum* day by generating a dynamic milieu at the cellular and the organismal level that oscillates with a circa-24-h rhythm. Beyond their function of generating daily rhythms, circadian clocks are sensors for environmental information that allows them to remain entrained to the regular changes of day and night, of light and dark, of warm and cold, of humidity and of all the resources that depend on these environmental changes (availability of food, presence of enemies and/or competitors etc.).

These regular changes have provided the selection pressures that have led to the development of circadian clocks very early on in evolution. The genes that are essential to make these endogenous clocks tick are not conserved across kingdoms (prokaryotes, unicellular eukaryotes, fungi, plants and animals), suggesting that these programmes have evolved several times during evolution. The recent discovery of non-transcriptional circadian oscillators (O’Neill and Reddy 2011; O’Neill et al. 2011) suggests, however, that a basic metabolic rhythm-generator may be ancestral to all circadian clocks, and that the specific transcriptional–translational mechanisms represent adaptations in the respective phyla.

1.1 A Clock with Many Names

The circadian system is referred to by many terms: oscillator, clock, pacemaker or temporal programme. The term ‘clock’ was used early on to describe the circadian programme and has strongly influenced our concepts, experimental approaches and interpretations of results (Roenneberg et al. 2008). Yet, the notion of a ‘clock’ evokes distinct associations: its hands always move with the same pace; it reliably represents time that we consult to take appropriate actions at the appropriate times;

its mechanism has to be compensated against temperature changes to keep the correct time. All these qualities of a physical clock were also associated with their biological counterparts.

In many cases, biological clocks are indeed used to 'read' the correct time, for example, in the dance 'language' of bees (Frisch 1967), the orientation of migrating birds (Gwinner 1996; Kramer 1952) or on the annual/seasonal time frame in photoperiodism (Bünning 1960). Temperature compensation is also a quality of biological clocks, since their free-running period does not change significantly with temperature (Hastings and Sweeney 1957); this quality was thus defined as one of the basic circadian properties (Roenneberg and Merrow 1998). Despite these apparent similarities, circadian clocks are not just mirror images of physical clocks. The velocity at which circadian clocks progress through their daily cycles is most probably not constant (Pittendrigh and Daan 1976; Roenneberg et al. 2010b), and temperature compensation of the free-running period does not mean that circadian clocks are insensitive to temperature changes; on the contrary, most of them can perfectly entrain to temperature cycles.

The circa-24-h rhythmicity is generated at the cellular level by molecular oscillators—based on transcriptional–translational mechanisms (Roenneberg and Merrow 2003), on metabolic feedback loops (O'Neill and Reddy 2011; O'Neill et al. 2011), or on their interaction. Molecular oscillators are not necessarily a circadian clock, which constitutes an organism's circadian programme (Pittendrigh 1993). In single-cell organisms, they fulfil the role of such a programme, although even at that level, several molecular oscillators can form a network (Baggs et al. 2009; Roenneberg and Morse 1993; Roenneberg and Merrow 2003). Although molecular oscillators are also found in virtually every cell of higher plants (Thain et al. 2000) and animals (O'Neill and Reddy 2011; Schibler et al. 2003), their circadian programme is an emergent property of the interactions between these oscillators. So, at all levels—from cells to organism—the circadian programme, which coordinates all functions to do the right thing at the right time within the 24-h day, involves many interacting oscillators, which all are part of the active synchronisation process called 'entrainment'.

1.2 Zeitgeber

Any environmental factor that varies across the 24-h day can potentially serve as an entraining signal (zeitgeber; German for 'time giver'). The evolutionary oldest clocks known are those in cyanobacteria (Johnson et al. 1996), photosynthesising prokaryotes. For photosynthesising organisms, light is both energy resource and zeitgeber. Thus, the oldest zeitgeber is an energy source and is some form of 'food'. As more clocks will be discovered in organisms that are not exposed to light–dark (LD) cycles and have so far been thought to be clock-less (e.g. those that live in the gut of a host), we may find that the rhythmic availability of 'food' can act as the primary zeitgeber. The single-cell organism *Lingulodinium* (former *Gonyaulax*) entrains to changing nutrient concentrations (e.g. nitrate; Roenneberg and Rehman 1996), and the clocks in mammalian liver cells synchronise to food (Stokkan et al. 2001). In contrast, the clock in the mammalian central pacemaker (the suprachiasmatic nucleus*;* SCN) appears to only use light as zeitgeber (Yamazaki et al. 2000), surrogated by transmitters released from collaterals of the optic nerves (van Esseveldt et al. 2000). Temperature is also a universal zeitgeber for circadian oscillators from single-cell organisms (Edmunds 1984) and fungi (Merrow et al. 1999) to tissue clocks in mammals (Brown et al. 2002; Buhr et al. 2010).

As much as the circadian clock of an organism has to entrain to its environment, the many cellular oscillators within an organism have to synchronise to their rhythmic internal milieu. In plants (Thain et al. 2000) and even in insects (Plautz et al. 1997), many entrain directly to light (i.e. by external time), while in mammals, for example, many signals can act as internal time cues (factors that fluctuate in the bloodstream, neuronal transmitters or body temperature; Dibner et al. 2010). Although any environmental factor that oscillates in a 24-h rhythm can act as a zeitgeber for different oscillators and under different conditions, light is the zeitgeber most abundantly used by circadian clocks. The reason for this dominant role is because light (and darkness) is responsible for all other environmental rhythms, and it is therefore the primary and most reliable source of information about time-of-day. Note that entrainment is an active process of the circadian system; the clock therefore *entrains to* rather than being *entrained by* a zeitgeber.

1.3 Input Feedback Loops: Zeitnehmer

The clock's rhythm generation and its sensory function are inseparable. Circadian programmes modulate their own input pathways at all levels—from the primary and secondary components of the reception pathway down to the molecules of the oscillator mechanism itself (Roenneberg and Merrow 2000, 2003). The environmental signals that allow the clock to actively entrain to the daily structure of the world are rhythmic and so is the machinery that senses them. We have therefore called these feedbacks, which are both input and output of the circadian system, *zeitnehmer* (German for 'time taker'; McWatters et al. 2000; Roenneberg et al. 1998).

The dual role of circadian clocks as rhythm generators and as sensors is especially obvious in the mammalian SCN. It generates circadian rhythms in many of its cells but also as a tightly coupled neuronal network and entrains to the LD cycle via retinal inputs (Rea 1998). As such, the SCN, which is often called the central pacemaker of the mammalian circadian system, serves predominantly as a relay station that transduces the information of light and darkness to the many other circadian oscillators in the body by providing endogenous 'zeitgebers' (Asher and Schibler 2011; Huang et al. 2011), which are more appropriately called *zeitnehmers*, since they are also both outputs and inputs of the circadian system.

The SCN's entrainment mechanism involves several *zeitnehmer* loops, on the molecular, the physiological and the behavioural level. It controls the (nocturnal) production of melatonin but is itself responsive to melatonin (Agez et al. 2009). It also controls the daily rhythm of core body temperature. All cellular clocks, including the cellular peripheral clocks in mammalian tissue cultures, can be entrained by temperature cycles (Brown et al. 2002). The question whether temperature constitutes yet another *zeitnehmer* loop in the entrainment process of the SCN is still open. Takahashi and colleagues argue that the strong coupling of the SCN neurones makes the central pacemaker resistant to temperature changes (Mohawk and Takahashi 2011). When the authors prevented coupling between SCN neurones (by applying tetrodotoxin), one-time 6-h temperature pulses strongly reset the phase of the rhythm while they had no effect on the intact, coupled network. This result shows that isolated temperature pulses presented to a system, which has stabilised in constant conditions, may not elicit phase shifts in a robust oscillator (e.g. a strongly coupled SNC network), yet it also highlights the limitations of using pulses for explaining entrainment. As will be discussed later, the PRC concept has greatly advanced our knowledge about entrainment (Comas et al. 2006, 2007, 2008; Daan and Pittendrigh 1976) but fails to fully explain this fundamental property of circadian clocks under all conditions (Rémi et al. 2010; Roenneberg et al. 2010a, b). The ineffectiveness of a single pulse does not necessarily exclude that the SCN's neuronal network can be entrained by continuous and gradual temperature changes as they occur under normal conditions.

Abraham and co-workers (2010) have shown both conceptually (by computer modelling) and by experiments in isolated tissues that temperature cycles are indeed capable to entrain the SCN, albeit with a smaller range of entrainment than in less strongly coupled networks (e.g. lung tissue). Thus, temperature forming a *zeitnehmer* loop in the entrainment of the mammalian clock cannot be ruled out. Such a feedback loop would include all functions that can change body temperature (e.g. activity, food intake or sleep).

2 Entrainment of the Human Clock

Entrainment is also the most important property of the human circadian clock, but as will be discussed later, modern conditions of living inside and using artificial light constitute momentous challenges to human environment. First, we will review two important questions pertaining to human entrainment (1) what is the intrinsic period of the human clock (commonly used as a basis for predicting entrainment) and (2) does the human clock entrain to social cues? In addition, we show how a simple questionnaire can be used to investigate human entrainment in the real world in thousands of people.

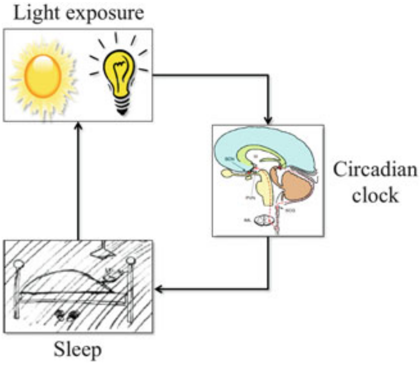

Fig. 1 Light exposure, the circadian clock and its output (the sleep–wake cycle) form a feedback loop in human entrainment

2.1 *What Is the Intrinsic Period of a Circadian Clock?*

Sleep itself is also an important behavioural *zeitnehmer* loop, because it influences the daily light profiles (by closing the eyelids, by retreating into a burrow or a dark room; Fig. 1). The fact that subjects in the Andechs bunker (Wever 1989) were allowed to switch off lights when they wanted to sleep has been identified as a problem for estimating the (*intrinsic*) free-running period. This self-created LD cycle prevents 'real' constant conditions, as they are thought to exist, for example, when recording rodents in constant darkness. However, the many *zeitnehmer* loops and oscillators that make up circadian systems are all an integral part of the entrainment process and may thus also influence the free-running period in constant darkness (τ_{DD}). The fact that rodents are active during their subjective night and sleep during their subjective day (with all the consequences, such as activity-/sleep-dependent temperature fluctuations or periodic food intake) makes an assessment of a 'true' *intrinsic* period questionable, even in DD because it is influenced by many other factors, for example, by the presence of a running wheel (Kuroda et al. 1997).

By making the self-sustained, free-running period a central quality/dogma of the circadian system (Pittendrigh 1960), the field has created a circular argument that has led to a selection of model organisms—namely, those which continue to show a robust rhythm in constant conditions. Theoretically, a damped clock would serve its functions perfectly in a cyclic environment, which periodically provides time cues that counteract dampening. We hypothesise that a self-sustained, free-running rhythm, measurable in constant conditions, is a consequence of a complex circadian system (including multiple oscillators and *zeitnehmer* loops). The interactions between the oscillators and the feedback provided by the *zeitnehmers* are the main reason for self-sustainment since they intrinsically provide rhythmic signals that prevent dampening. Steinlechner and colleagues have shown that the ability to free-run is challenged in clock mutants (Steinlechner et al. 2002) when they are kept in DD but not in LL. The most simple explanation for this observation is that the *zeitnehmer* feedback of the sleep–wake cycle (as shown in Fig. 1) is much stronger when this behaviour involves modulations of light levels and therefore can turn a challenged (damped) circadian clock into a self-sustained rhythm in LL.

Circadian clocks have evolved to produce an *internal day* representing the external day. This is different to evolving a specific intrinsic free-running period (τ), for which there was no selection pressure. A steady-state τ in artificial constant conditions can only be reliably assessed when measured over several days and thus represents the average *internal day* that the circadian system produces under a given condition. τ is subject to the influence of many factors—beyond DD or LL (of different intensities)—and many of these (e.g. wheel running) will affect different *zeitnehmers* within the system and thereby change τ. While this average *internal day* (τ) is not reliable to predict entrainment under all conditions (Rémi et al. 2010), we must presume that every circadian clock produces its individual *internal day* based on genetic background. The *internal day* indeed forms the basis for entrainment, but the genetic background of an organism/individual will also influence many other aspects of the circadian machinery—from inputs via *zeitnehmers* to outputs. The difficulty of this concept is that the length of an individual clock's *internal day* cannot be measured experimentally since the entraining mechanisms will also be active in constant conditions (e.g. will be the influenced by *zeitnehmers*) and thereby change τ. Thus, the length of an *internal day* can only be assessed theoretically (see, e.g., Czeisler et al. 1999; Roenneberg et al. 2010a).

2.2 Social Zeitgebers

The notion that humans can entrain to non-photic, social cues goes back to the pioneering experiments in the Andechs 'bunker' (Wever 1979), showing that the human clock can entrain even to regular gong signals. The question whether social signals can act as zeitgebers for the human clock can best be answered by studying blind people. There are different types of blindness (1) lack of visual perception, (2) lack of residual light perception and (3) lack of physiological light responses (e.g. suppression of melatonin or pupillary reactions). While circadian rhythms in individuals of the first two types of blindness still entrain to light–dark cycles, the clocks of those, who suffer from the third type of blindness, are often not entrained [evidenced by measuring melatonin or core body temperature profiles (Sack et al. 1992)]. That their clocks run free in real life is remarkable because these individuals are submitted to strong social 24-h time cues. It suggests that the influence of non-photic zeitgebers on human clocks depends on functional light perception [even if unconscious (Zaidi et al. 2007)]. Thus, successful entrainment to non-photic time cues is apparently achieved via the behavioural *zeitnehmer* loop shown in Fig. 1 (Czeisler et al. 1986; Honma et al. 2003), indicating that the human clock does not entrain directly to social signals—otherwise blind people of all three types could successfully entrain to 24-h cycles.

Yet, how could this hypothesis explain the fact that some blind individuals of the third type—that is, without any light perception—are able to live a 24-h day (Czeisler et al. 1995; Lockley et al. 1997; Sack et al. 1992)? One possible explanation is that the length of their *internal days* is already close to 24 h. This would allow them to synchronise to relatively weak, non-photic time cues, for example, to activity-dependent temperature changes and/or to regular meals (Klerman et al. 1998; Mistlberger and Skene 2005). That non-photic signals can indeed contribute to entrainment has also been shown in the Andechs bunker experiments: the range of entrainment under LD cycles became larger when regular acoustic signals (regulating sleep–wake behaviour) were added to the protocol (Wever 1979). It follows that synchronised blind people of the third type of blindness would fail to entrain if they were exposed to schedules longer or shorter than 24 h and, conversely, that totally blind people, who do not entrain in real life, would synchronise to schedules that are closer to the length of their *internal days*.

The example of entrainment in blind individuals shows that light is also the dominant zeitgeber for human entrainment. It also suggests that entrainment may indeed involve multiple zeitgebers acting in concert, despite being insufficient—each on their own—to ensure entrainment.

2.3 Constant Versus Entrained Conditions

The fact that every organism adapts its physiology and behaviour to the alternation of day and night appeared so trivial that scientists have not seriously investigated this phenomenon until the nineteenth century [except for de Mairan (De Mairan 1729)]. The insight (and proof) that an endogenous mechanism governs the daily changes in metabolism, physiology and behaviour was only possible by experiments performed in constant conditions, showing that circadian clocks maintain a self-sustained rhythm, albeit not with an exact 24-h period.

This discovery has dominated how researchers investigate and think about circadian clocks. The focus of circadian research on free-running rhythms is overwhelming although the clock hardly ever had the chance to evolve without the presence of zeitgebers (Roenneberg and Merrow 2002). Laboratory experiments (especially those investigating the molecular mechanisms of the clock) rarely use entrainment protocols. The traditional models of entrainment assume a basic free-running period (τ) and then apply mechanisms that correct its difference to the zeitgeber period (T) by regular resets of the rhythm's phase, so that the periods of clock and zeitgeber become identical ($T - \tau = 0$). As discussed above, this assumption is correct, if based on the length of the *internal day* ($|_{\mathrm{E}}$) but not necessarily if based on $|_{\mathrm{DD}}$ or $|_{\mathrm{LL}}$. Traditionally, the clock's response to light is probed experimentally by applying singular light pulses at different circadian times in DD and thereby establishing a so-called phase response curve (PRC) (Hastings and Sweeney 1958). Although PRCs have been instrumental in our understanding of entrainment (Comas et al. 2006, 2007, 2008), there are two difficulties with explaining entrainment by singular events (e.g. a light pulse or a light–dark transition). First, it makes predictions of entrained phase in a noisy photic world extremely difficult (such predictions strictly would need to be based on PRCs generated separately for every change in intensity). Second, it puts the cart before the horse by assuming that evolution has produced an intrinsic period in constant conditions (which we have already ruled out above) and then added a mechanism to compensate for its 'inaccuracy'.

We have recently addressed the first difficulty and proposed that the circadian clock integrates light over the course of a day, which can be formally quantified by a circadian integrative response characteristic (CiRC) Roenneberg et al. 2010b). The CiRC is merely an extension of the pioneering work that leads to the establishment and perfection of the PRC (Comas et al. 2006, 2007, 2008; Daan and Pittendrigh 1976; Hastings and Sweeney 1958). But despite similar in shape to the traditional PRC, the CiRC differs in one important quality: it makes no assumptions about the mechanism that synchronises τ with T, that is, it does not presume an instantaneous response every time light levels change (phase shifts or a velocity changes). It integrates the light exposure over the past 24 h and calculates its effect on the current length of the *internal day* (τ_E). Based on the shape of PRCs, the CiRC presumes that light exposures around dawn compress and those around dusk expand the *internal day*.

In a series of experiments with the fungus *Neurospora crassa* (varying photoperiod, τ and T) (Rémi et al. 2010), we showed that only the CiRC and not the PRC can accurately predict the phase of entrainment under all applied conditions (Roenneberg et al. 2010a). The assumption that the entrainment process is based on light integration rather than on a differential detection of light changes is supported by the discovery of the circadian photoreceptor melanopsin (Freedman et al. 1999; Provencio et al. 2000). Melanopsin functions as a light integrator rather than a change detector (Lucas et al. 2003).

We still have to address the second, more fundamental difficulty. As argued above, evolution must have acted on the entrainment mechanism—genetic differences produce different CiRCs that result in individual-specific phases of entrainment, earlier or later. It follows that the observed differences in τ are a consequence rather than the basis of this genetic variability (Roenneberg and Merrow 2002). We are in the process of moving the horse back in front of the cart but still have to go a long way until we understand entrainment.

The best way to investigate entrainment is using entraining conditions, either by analysing steady-state entrainment in the laboratory (e.g. Abraham et al. 2010) or by measuring circadian properties in the real world. More recent work in mice and *Drosophila* has shown that the temporal behaviour of the classical model organisms, which have been extensively investigated in the laboratory, can be astonishingly different when measured under natural conditions (e.g. Bachleitner et al. 2007; Daan et al. 2011; Peschel and Helfrich-Forster 2011; Vanin et al. 2012).

2.4 Phase of Entrainment: Chronotype

Investigating the human clock under entrainment rather than in constant conditions has big advantages. Experiments in temporal isolation are both extremely cost- and labour-intensive (and can therefore only include few subjects). In contrast, assessing phase of entrainment by questionnaires (based on sleep times; chronotype) allows to investigate thousands of people in real life. The first instrument developed for assessing temporal sleep preferences was the morningness–eveningness questionnaire (MEQ) (Horne and Östberg 1976), which produces a score (high values indicating morning types and low values evening types). A score-based analysis is useful when chronotype is regarded as a psychological trait, and the MEQ-scores do correlate with sleep times (Zavada et al. 2005). However, when chronotype is used as a measure for entrained phase, its assessment should ideally be time- and not score-based (Roenneberg 2012). To this end, we developed a questionnaire (the Munich ChronoType Questionnaire, MCTQ), which asks simple questions about sleep behaviour separately for workdays and free days (Roenneberg et al. 2003).

Since the year 2000, the MCTQ is accessible online (http://www.theWeP.org), and the database of the ongoing MCTQ project has now exceeded 150,000 entries. Participants receive an email containing a PDF that provides individual feedback on how their results (chronotype, sleep duration, etc.) compare to those of the population stored in the database. This individualised feedback is most probably the key to the project's success. The MCTQ is available in several languages (English, German, French, Dutch, Spanish, Portuguese, Danish, Turkish, with more language variants being developed). So far, the majority of entries are from central Europe (Germany: 70 %; The Netherlands: 12 %; Switzerland 6 %; Austria: 4 %; UK 1 %; Hungary: 0.6 %; France and Italy: 0.3 %; Belgium, Spain, and Sweden: 0.2 %). In Germany, The Netherlands, Switzerland and Austria, between 0.05 and 0.08 % of the total population have filled out the MCTQ. The long-term aim of this project is to create a world-sleep-map (Fig. 2) that allows separating cultural, geographical and climatic influences from actual light entrainment.

Chronotype is assessed as the mid-phase of sleep on free days (MSF), corrected for 'oversleep' due to the sleep debt that individuals accumulate over the workweek (MSF_{sc}) (Wittmann et al. 2006). The variables of the MCTQ have been validated against sleep-logs, actigraphy, as well as cortisol and melatonin profiles measured in constant routines (Roenneberg et al. 2004 and manuscript in preparation). All these validations show highly significant correlations with chronotype assessed by the MCTQ. But does this marker represent an individual's phase of entrainment (¬)?

The internal phase relationships between different circadian outputs are not fixed. Therefore, chronotype strictly only represents Ψ of the sleep–wake cycle and not even Ψ of the activity–rest rhythm under all conditions. We have shown for example that these two rhythms respond differently to the changes in and out of daylight savings time (Kantermann et al. 2007). The internal phase relationship between the

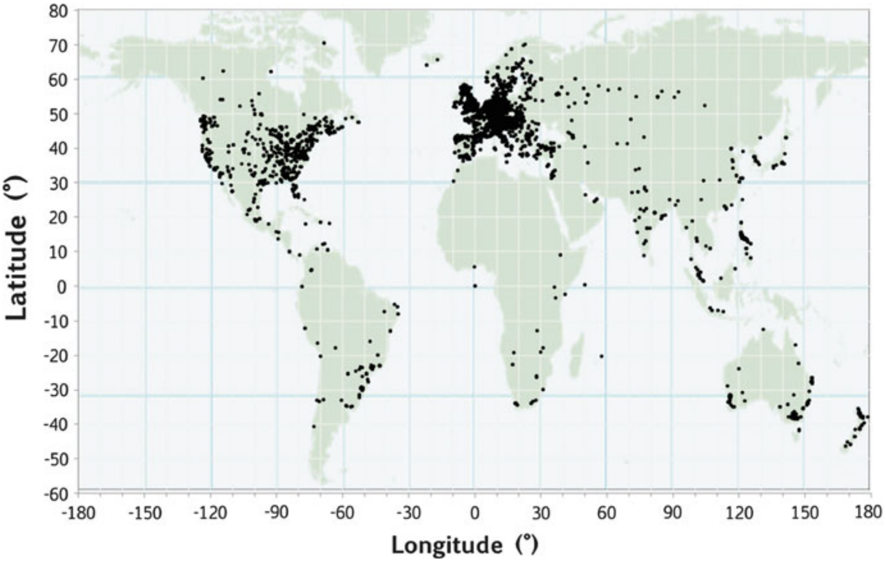

Fig. 2 Global locations of MCTQ entries. Central Europe has by far the highest representation in the database, but entries from the Americas, Asia, Oceania and to some extent from Africa are beginning to accumulate (the *dots* in the middle of oceans represent islands such as Mauritius, the Seychelles or Sao Tome). Source of the equidistant cylindrical projection of the world: http://kartoweb.itc.nl/geometrics/Map%20projections/body.htm

sleep–wake cycle and other circadian variables (e.g. melatonin or core body temperature, CBT) may vary substantially. While mid-sleep in humans is centred approximately around the time of the CBT minimum under entrained conditions, sleep is generally initiated at the time of the CBT minimum in temporal isolation (Strogatz 1987; Wever 1979). Depending on conditions, different chronotypes may also show different internal phase relationships between melatonin and sleep (Chang et al. 2009; Duffy et al. 2002; Mongrain et al. 2004).

The analysis of the growing MCTQ database has produced many important insights into human sleep–wake behaviour (for reviews, see Roenneberg and Merrow 2007; Roenneberg et al. 2007b). The most important feature of the MCTQ turned out to be the separate enquiry of sleep times on workdays and free days (see also the section on *social jetlag* below). Our analysis has clearly shown that sleep timing (chronotype) and sleep duration are separate traits. There are as many short and long sleepers among early chronotypes as there are among late chronotypes. However, when sleep behaviour is analysed separately for workdays and free days, sleep duration clearly depends on chronotype. The later their chronotype, the less sleep people get on workdays and the longer they sleep on their free days (as a compensation for the sleep debt they have accumulated during the workweek) (Roenneberg et al. 2007b).

Little is known about the mechanisms that underlie the large variability in chronotype and sleep duration. Overwhelming evidence from experiments in rodents has shown that the timing of sleep and activity depends on variants and mutations of clock genes (see for example, Steinlechner et al. 2002). Although rodents are nocturnal and do not show the same consolidation of sleep as our species does, one can infer that human chronotype has also a genetic component (Brown et al. 2008). Indeed, several studies have shown that chronotype depends on variants of human clock genes (Jones et al. 1999; Toh et al. 2001; Xu et al. 2005). A genetic predisposition has also been shown for human sleep duration (Allebrandt et al. 2011a, b).

Besides a genetic influence, chronotype depends on several other factors, for example, on development. Children are generally early chronotypes up to the age of 14 and then significantly delay during puberty and adolescence. From the age of 20 onwards (19.5 in women and 21 in men), the entrained phase of the sleep–wake cycle is progressively advanced again until chronotype in the elderly becomes as early as in children (Roenneberg et al. 2004). The changes in chronotype between the age of 16 and 22 are often dismissed as ‘typical adolescent behaviour’, but Mary Carskadon argues that this change is associated with an age that used to represent the height of reproductive behaviour and that moving sleep times away from the rest of the (younger and older) population opens up a distinct temporal niche (Carskadon 2011). A recent review shows that changes in circadian timing are also found in animals, strengthening the hypothesis that this change is based on biology and not merely peer pressure (Hagenauer and Lee 2012).

Besides genes, sex and age, light exposure is another factor that determines chronotype and is subject to the following paragraph.

2.5 Light as Zeitgeber for the Human Clock

The question whether the human clock entrains to social zeitgebers or predominantly to light has been addressed above in relationship to entrainment or rather to the lack of entrainment in blind people. We have used the MCTQ database to answer this question from a different angle (Roenneberg et al. 2007a): do people within the same country live according to local time or according to the light–dark cycle? At the time of the study, the database contained approximately 40,000 German entries, including place of residence and postal code, which allowed us to reconstruct the geographical locations (Fig. 3). We then calculated the average chronotype (MSF, normalised for sleep debt, age and sex) for each longitude. Germany extends over nine latitudinal degrees, so that the sun rises 36 min earlier at the country’s eastern edge than at its western edge. If the human clock entrained to social time, all Germans should have on average similar chronotypes—independent of longitude; if it however entrained to the light–dark cycle, average chronotype in each longitudinal slice should be four minutes later per longitude from east to west. The results of this ‘experiment’ were absolutely clear: entrainment of the human clock depends on sun time and not on local (social) time.

Although the average chronotype of people living in larger cities is later and the latitudinal slopes are flatter, chronotype still significantly correlates with sunrise.

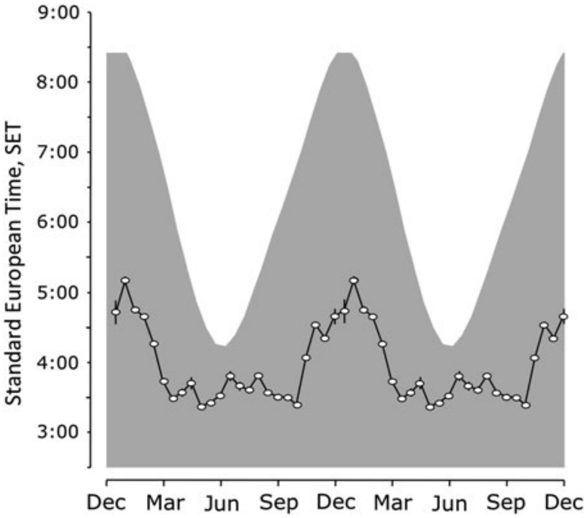

Fig. 3 Each of the locations shown on the map to the *right* represents up to several hundred entries. Their number strongly correlates with the population density of the respective location. The *horizontal axis* represents the local time of sunrise for each longitude on the longest day of the year (as reference). The *vertical axis* shows the local time of the average chronotype (MSF*sc*, normalised for age and sex) for each longitude. The stippled diagonal represents the east–west progress of sunrise. The *different symbols* represent locations with different population size; *dots*: ≤300,000; *squares*: 300,000–500,000; *triangles* >500,000 [$N \approx 40{,}000$; redrawn from Kantermann et al. (2007)]

The fact that this relationship depends on population size could be explained by different light exposure in these locations. The smaller a town, the more time people spend outdoors (e.g. access to gardens and balconies, commutes by bike or by foot) and the lower the artificial light levels at night. The greater the differences between light and darkness, the stronger the zeitgeber and the earlier the phase of entrainment (at least for the vast majority of people whose circadian clocks produce *internal days* longer than 24 h).

The MCTQ also asks how much time people spend outdoors without a roof above their heads during daylight. The analysis of this question shows that chronotype is progressively advanced the more time people spend outdoors (Fig. 4). The German latitude study has clearly shown that the human clock entrains to sunlight and not to social cues, but it did not specify which part of the light–dark cycle is most important for human entrainment (e.g. dawn or dusk). Since dawn and dusk move in opposite directions with waxing and waning photoperiod, this question can be answered by investigating the seasonality of chronotype. The results show that chronotype is aligned to dawn during winter and spring and appears to be independent of dawn or dusk during summer and autumn (Fig. 5). The fact that people are on average later chronotypes in winter is probably due to a combination of longer nights, later dawn and reduced light exposure.

The reason for these dependencies varying with season may be a combination of (1) daylight savings time (DST), of (2) the fact that locking sleep to dawn throughout the year would mean that one has to fall asleep at around 7 p.m. (local DST

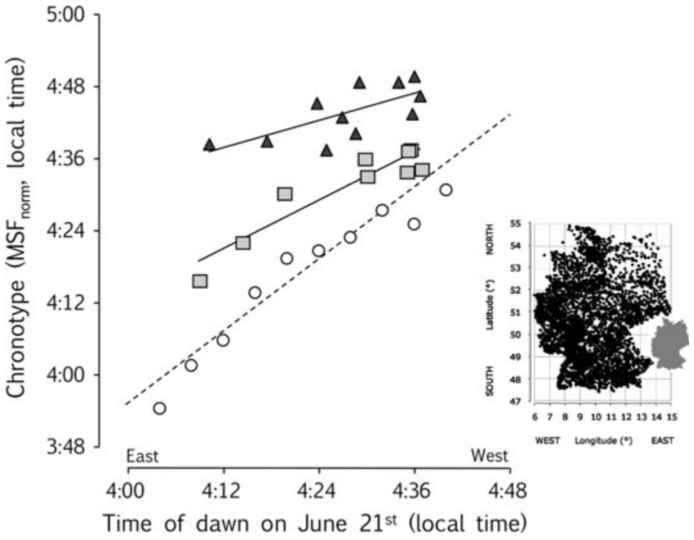

Fig. 4 With increasing time spent outdoors (during the day), the phase of entrainment advances. The strongest effects are up to an outdoor light exposure of two hours, advancing the phase by more than 2 h [$N \approx 41{,}000$; redrawn from Roenneberg and Merrow (2007)]

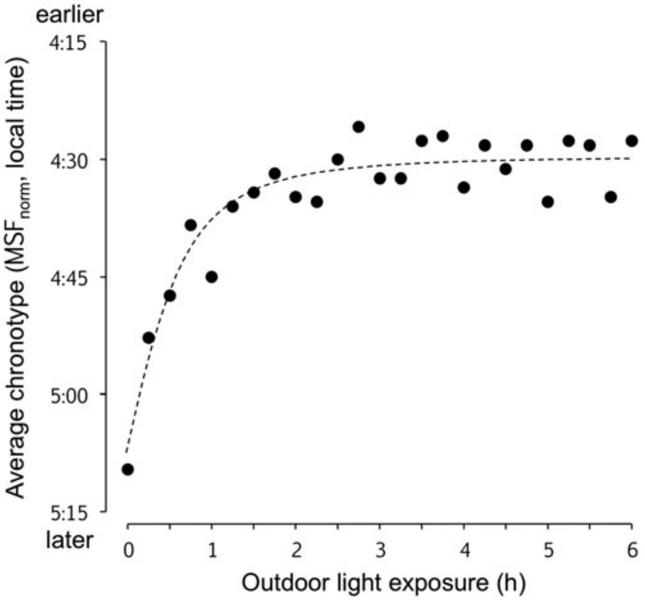

Fig. 5 Seasonal changes in phase of entrainment. *Dots* represent average chronotype (y-axis; expressed in Standard European Time, i.e., ignoring DST changes) across the year in half-month bins (x-axis). The edge of the *grey area* represents average sunrise times in Central Europe [$N \approx 55{,}000$; redrawn from Kantermann et al. (2007)]

time) in midsummer to get an average of 8 h of sleep, and (3) that in long photoperiods the time difference between dusk and dawn becomes too short, so that both factors influence phase of entrainment.

2.6 The Concept of Social Jetlag

The majority of the population represented in the MCTQ database shows large differences in sleep behaviour between workdays and free days—both in duration and timing. We have proposed that these differences represent the discrepancy *internal* and *external* time, between the control of the circadian clock and that of the social clock (predominantly set by work schedules). To quantify this phenomenon, which we have coined *social jetlag* (Wittmann et al. 2006), we calculate the difference between mid-sleep time on workdays (MSW) and on free days (MSF; Fig. 6). The example shown in Fig. 6 is extreme (a late chronotype with an early work start), but the majority of the population shows similar patterns.

Although one can sleep outside the temporal window provided by the circadian clock (e.g. naps), sleep is more efficient when coinciding with the circadian window (Wyatt et al. 1999). Around 80 % of the regularly working individuals represented in our database use alarm clocks on workdays. This premature interruption of sleep results in sleep loss (especially in the later chronotypes), because the circadian clock strongly influences when one can fall asleep. To compensate for the sleep debt accumulated over the workweek, people commonly ‘oversleep’ on free days (Fig. 6). While alarm clocks are the predominant cause for sleep loss in later chronotypes, social pressures to stay up later than their biological bedtime commonly causes sleep loss in early chronotypes. The majority of the Central European population in our database goes to bed at 11 p.m. or later (64 % on workdays and 90 % on free days).

Shorter habitual sleep has been shown to be associated with greater sleep debt (sleep pressure) in the sleep laboratory, indicating that interindividual habitual sleep duration primarily reflects self-selected sleep restriction (Klerman and Dijk 2005). While late types can compensate for this sleep loss on free days by ‘sleeping in’, early types are woken up by their circadian clock and can therefore only compensate their sleep loss by resisting the social pressure of the late majority.

The term *social jetlag* is based on the observation that sleep timing between workdays and free days resembles the situation of travelling across several time zones to the West on Friday evenings and ‘flying’ back on Monday mornings (Fig. 6). The symptoms of jetlag (e.g. problems in sleep, digestion and performance) are manifestations of a misaligned circadian system. In travel-induced jetlag, these complaints are transient until the circadian clock has re-entrained to the light–dark cycle at the destiny. In contrast, social jetlag is a chronic phenomenon, lasting throughout an individual’s working life. 69 % of the working population represented in our MCTQ database experience at least one hour of *social jetlag* and one-third suffer from 2 h or more. Notably, the larger the discrepancy between internal and

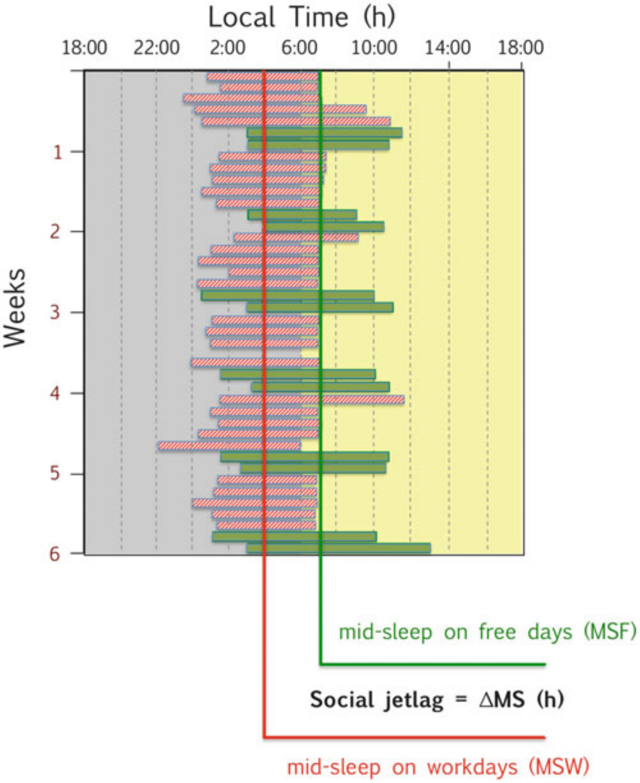

Fig. 6 Six-week long sleep-log of an extremely late chronotype (MSF ≈ 7), exemplifying the typical scalloping between sleep on workdays and on free days (*horizontal axis*: local time; *vertical axis*: days of the sleep-log. The *bars* show the timing and duration of sleep on the respective days (*red*: workdays; *green*: free days). The difference between the mid-sleep point on free days, MSF) and that on workdays (MSW) is used to quantify social jetlag. Note how sleep on workdays is interrupted by the alarm clock (constant sleep end at around 7 a.m., corresponding to internal mid-sleep of this subject)

external timing in an individual, the more likely he/she is a smoker (Wittmann et al. 2006) and the more alcohol and caffeine he/she consumes (Till Roenneberg, unpublished). In addition, every hour of social jetlag increases the chances to be overweight/obese by 30 % (Roenneberg et al. 2012).

3 Concluding Remarks

The importance of light as a zeitgeber has been well documented for virtually all plants and animals but was long debated for humans. The results of our epidemiological studies have clearly shown that the human clock entrains to light. As to be expected for a day-active species, dawn appears to be more important than dusk for human entrainment (except in short summer nights). The fact that the correlation between ‘unforced’ sleep timing (e.g. on weekends) and dawn becomes flatter with growing urbanity indicates a historical change in human entrainment. In rural societies and probably throughout most of human evolution, the predominant zeitgeber was environmental light and darkness. With increasing urbanisation, which goes hand in hand with a decreasing exposure to outside light (Roenneberg et al. 2012) and an increasing self-control of the immediate light environment, human entrainment has become sleep-centric. Both sleep per se (i.e. closing our lids and rolling up our eye balls) and bedroom behaviour (retreating into darkness) are becoming the most important dark-signals that entrain the human clock (see Fig. 1). Thus, *zeitnehmers* potentially become more important to human entrainment than zeitgebers. This new situation in our evolution predicts that even sighted people, who are not solidly embedded in a social context and rarely expose themselves to the natural light–dark cycle, may be not entrained. This has already been reported for isolated cases as well as for psychiatric patients (Wulff et al. 2010).

Our epidemiological results show that social and biological time are increasingly drifting apart (*social jetlag*). The insight that sun time is more important to human temporal biology than social time has to be taken seriously by decision-makers. For example, the introduction of daylight savings time (DST), that is, making people go to work an hour earlier in summer than in winter, greatly increases *social jetlag*. Another source for *social jetlag* is the fact that work schedules have not changed significantly since our rural past, while chronotype of individuals living in industrialised regions has become too late to comply with the usual beginning of work; this has made the usage of alarm clocks reach epidemic scales. *Social jetlag* is a small but chronic version of shift-work or circadian misalignment (Scheer et al. 2009), resulting in chronic sleep restriction, substance abuse and metabolic challenges (Roenneberg et al. 2012; Wittmann et al. 2006). It is as though the majority of the population is working the early shift with all the known side effects of shift-work on health, performance and wellbeing. While ‘forced desynchrony’ is an important protocol in circadian laboratory experiments, one could argue that society runs a huge real-life experiment of ‘forced synchrony’.

Acknowledgments Our work was supported by the FP6 programme EUCLOCK (TR, KVA), by the Siemens AG (TR, CV, MJ) and by the German Research Foundation (DFG; TK).

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