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THEORETICAL REVIEW

Live to the rhythm, slave to the rhythm ☆

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Summary Circadian rhythms in health and disease have most often been described in terms of their phases and amplitudes, and how these respond to a single exposure to stimuli denoted as zeitgebers. The present paper argues that it is also important to consider the 24-h regularity in the repeated occurrence of the zeitgebers. The effect of the regularity of stimulation by light, melatonin, physical activity, body temperature, corticosteroids and feeding on synchronization within and between the central circadian clock and peripheral oscillators is discussed. In contrast to the phase shifts that can be recorded acutely after a single zeitgeber pulse, the effects of irregularly versus regularly timed zeitgeber can be studied only in long-term protocols and may develop slowly, which is a possible reason why they have received relatively little attention. Several observations indicate a reciprocal relation between the robustness of the endogenous circadian timing system and its dependency on regularly timed zeitgebers. Especially at old age and in disease, proper functioning of the circadian timing system may become more dependent on regularly timed exposure to zeitgeber stimuli. in such conditions, regularly timed exposure to zeitgeber appears to be highly important for health. After a concise introduction on inputs to the central and peripheral oscillators of the circadian timing system, the paper discusses the responses of the circadian timing system and health to (1) a chronic lack of zeitgeber stimuli; (2) fragmented or quasi-ultradian stimuli and (3) repeated phase shifts in stimuli. Subsequently, the specific relevance to aging is discussed, followed by an overview of the effects of experimentally imposed regularly timed stimuli. Finally, a possible mechanism for the gradually evolving effects of repeated regularly timed stimuli on the circadian timing system is proposed.

☆ Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

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Introduction

Some may associate the title of this manuscript with long forgotten times, with a dance floor, swinging to the syncopated timing of a 1985 song of singer Grace Jones. Her call to live to the rhythm was only a few years after punk rock musicians, following James Dean's adage, expressed their preference to live fast and die young. Some readers may recognize these music scenes; others may have been too young or old to remember, maybe at the age of getting pushed on a swing by their parents, or the other way around, busy pushing their own child on a swing. What does all this have to do with circadian rhythms? The answer will develop in the discourse of this manuscript, which focuses on how *repeated*, *regular time cues* may affect circadian rhythms, and their sequelae for health and well-being, with special relevance to aging.

Many excellent reviews have discussed the complex mechanisms of the central and peripheral oscillators that make up the circadian timing system (CTS) (e.g.[1,2]). It is not the aim of the present paper to add another comprehensive review. Rather, the focus will here be on the specific question of what the consequences might be of a *lack* of input or *irregular* (versus regular) input impinging on the central and peripheral clocks. To explain what regular versus irregular input means, let us first consider a metaphor. Imagine a child playing on a swing (Figure 1). By stretching and contracting the legs at specific times during the oscillation, and thus systematically raising and lowering its center of mass, the child can continue swinging, i.e. sustain the oscillation, as long as he desires. This swinging behavior is known as a parametric oscillation and can be described with a mathematical function. One could regard this as comparable to a *self-sustained oscillator*, or an *endogenous clock*. Experienced children can get into such oscillation by themselves without any push. Well-timed *regular* pushing still does help them however. This pushing can be regarded comparable to, in circadian terminology, a *zeitgeber*. A child that does not master the specific leg movement yet is even completely dependent on such regular pushing. In this case, if one stops to push, the oscillation will dampen and

Figure 1 Child on a swing, a metaphor of the oscillations and required internal and external drives.

eventually stop. One could regard this comparable to a *non-self-sustained or dampened oscillator*.

Now suppose that the pusher advances the timing of each push, yet keeping the same time interval. This initially disrupts the smoothness and amplitude of the swing oscillation a little, but after a while, it regains its strong amplitude, *resynchronized* to the *phase* of the new push timing. One could regard this as a *phase-advance*, and a similar scenario could be sketched to obtain a *phase-delay*. The swinging child re-*entrains* to an altered *zeitgeber* timing.

The present review focusses on the following part of the metaphor. Suppose that the pusher is *really* distracted by other interesting on goings in the play garden, consequently does not pay attention to the timing of the push anymore, and as a result often forgets to push, pushes too early and pushes too late. What will happen to the swing oscillation? If the child masters the systematically timed stretching and contracting of the legs very well, it will continue to swing, be it less smooth and comfortably. But if the child does not master the essential movements too well, the oscillation will become erratic, its amplitude will decrease, and possibly the swing even comes to a halt. One could regard this as a metaphor for the first hypothesis here stated; that with *irregularly timed zeitgeber* a *robust* rhythm can only be accomplished by a *strong endogenous oscillator*. The less strong the *endogenous oscillator* is, the more the vulnerable the oscillation will be to a lack of, or erratic, *external stimuli*, leading to erratic oscillations and damping.

Another scenario that could also lead to erratic swinging and damping is when the child makes wrongly timed leg movements. What will happen to the swing oscillation in this case? If a parent pushes adequately, this will counteract the damping effect of the erroneous leg movements, and the child will continue to swing, be it less comfortably. But if the parent does not push regularly, the oscillation will clearly become erratic, its amplitude will decrease, and possibly the swing even comes to a halt. One could regard this as a metaphor for the second hypothesis here stated; that with a *weak endogenous oscillator* a *robust* rhythm can only be accomplished by a *strong and regularly timed zeitgeber*. The less strong the *external zeitgeber* is, the more vulnerable the oscillation will be to *internal disturbances*, leading to erratic oscillations and damping.

Most of the experimental studies on biological rhythms have either applied a single pulse of a zeitgeber, or repeated identical pulses, to evaluate their effect on the amplitude, phase and phase synchronization of central and peripheral clocks. We here argue that it is worthwhile to also consider the effects of (1) a *chronic lack* of pulses, (2) *multiple* (ultradian) pulses and (3) pulses of *variable* timing, and that doing so may provide a new view on equivocal findings in diseases where involvement of a malfunctioning CTS has been proposed.

The examples that will be given in this manuscript by no means represent a comprehensive review of all relevant studies. They serve to give examples supporting the relevance of investigating prolonged exposure to unusual zeitgeber patterns—be it a lack of circadian modulation, an ultradian pattern, or a non-24 h pattern. Such patterns could have strong implications for clock functions.

After a concise introduction on inputs to the central and peripheral oscillators of the CTS, the paper discusses the responses of the CTS and health to (1) a chronic lack of zeitgeber stimuli; (2) fragmented or quasi-ultradian stimuli; and (3) repeated phase shifts in stimuli. Subsequently, the specific relevance to aging is discussed, followed by an overview of the effects of experimentally imposed regularly timed stimuli. Finally, a possible mechanism for the gradually evolving effects of repeated regularly timed stimuli on the CTS is proposed.

The CTS and its synchronizing inputs in a nutshell

All life has evolved in environments with continuously changing temperatures and light intensities, cycling at a rate of 24 h. It is therefore not surprising that rhythms of about 24 h, i.e. circadian, are integrated in all processes of life, including gene expression, the biochemical processes in a cell, the complex physiology of an organism, its behavior and cognitive processes. A complex system of central and peripheral oscillators is responsible for this circadian modulation of our bodily functions.

Although we are seldom aware of the circadian modulations of our functions, they are continuously present, and continuously modulated by external inputs. Perhaps the most remarkable about *the central oscillator*, which resides in the hypothalamic suprachiasmatic nucleus (SCN) in all mammals, is that it can do without *any* timed input and still show a clear circadian rhythm in its cellular biochemical, electrophysiological and network interaction activity. In terms of the metaphor of a child on a swing, this is a child that masters the systematic raising and lowering its center of mass

enabling it to sustain the parametric oscillation as long as it desires to. The SCN thus contains a true endogenous pacemaker. However, under normal conditions in an intact animal, the SCN continuously receives input that is modulated by changes in the intensity of environmental light, in body temperature, in melatonin level, in the level of physical activity, and possibly other processes as well.

We do become aware, at least indirectly, of circadian modulations of our functions if they become disrupted. Anyone who has traveled multiple time zones or has been working on a shift work schedule is at least familiar of the physical discomfort induced by desynchronization between the internal physiological clockworks and the behavior required by the environmental clock time. Such desynchronization leads to disrupted regulation of sleep and wakefulness, body temperature, blood pressure, hormone production, digestion and immune activity. Luckily, the central pacemaker in the SCN shows a high plasticity with regard to its timing, allowing its oscillations to resynchronize to changes in the environmental light–dark (LD) cycle. The SCN makes use of so-called zeitgebers to accomplish such resynchronization. Environmental light, especially light of high intensity, may be the most salient zeitgeber. 'Zeitgeber effects' on the clock have also been demonstrated for melatonin (reviewed in[3]), for activity (e.g.[4]) and for temperature pulses (reviewed in[5]). The effects of light and temperature make sense from an evolutionary perspective: ever since life emerged, organisms and their CTS have evolved under the ever present ~24-h rhythm in environmental light and temperature.

In order to regain an optimal orchestration of the bodily physiological processes, it is not sufficient that the central clock in the SCN resynchronizes to the shifted timing of environmental demands: oscillators in peripheral organs need to follow-up on this shift in order to regain synchrony both with the master clock and among each other. Peripheral clocks are under the hierarchical dominance of the SCN, and have therefore also been called 'slave oscillators'. The coherence between the phases of different peripheral clocks disappears in mice with SCN ablations.[6] In contrast to the self-sustained oscillator in the SCN, rhythms in peripheral clocks can sustain autonomously only for some days, but ultimately disappear without daily enforcement originating in the SCN.[7] In terms of the metaphor of a child on a swing, these are the kids that do not master the systematic raising and lowering of their center of mass, and can swing only if being pushed regularly, with a specific timing. The enforcing process by which the SCN accomplishes this involves both neuroendocrine mechanisms and the peripheral autonomic nervous system outputs.[8] Stratmann and Schibler[2] recently reviewed the most important *signaling pathways* originating in the SCN *that synchronize peripheral oscillators* in remote organs. A key candidate among blood-borne factors that could affect peripheral oscillators is glucocorticoid hormone. A second key signaling pathway is the rest–activity rhythm, and possibly even more important the resulting rhythm in feeding and fasting. A third important signaling pathway could be body temperature, of which the endogenous circadian modulation is amplified by the circadian modulation of activity, posture and feeding.[2,5,9,10]

The process of resynchronization of peripheral clocks may develop differentially for different organs and stimuli, and even for different aspects of a single regulated system. An example of the latter is that, following a 7-h phase shift, the acrophase of the ACTH and cortisol rhythms are resynchronized by 10 days, whereas the nadir of the same rhythms takes 3 weeks to resynchronize.[11] Another example of different rates of synchronization within one system is that after a reversal of the LD cycle, resynchronization of clock gene expression oscillations in the heart takes at least 3–5 days, whereas behavior and heart rate resynchronize within 1–2 days.[12] As a consequence, the molecular machinery of the heart cells is suboptimally synchronized to their output function for several days. A differential resynchronization to an abrupt change in feeding time has been reported by Damiola et al.[13] who showed that phase-resetting occurred faster in the liver than in the kidney, heart or pancreas. The term 'internal desynchrony' has often been used to describe the phenomenon of (transiently) uncoupled rhythms. The examples above indicate that the synchronization of slave oscillators with each other and with the master clock can be a slow and delicate process, requiring many regular 24-h cycles of input before a complete stabilization is reached. As a consequence, a first plausible hypothesis is that the synchronization with the central pacemaker and among peripheral oscillators would be served best by a *sustained regular* 24-h zeitgeber input pattern.

Peripheral clocks likely play an important role in the function and viability of peripheral organs. For example, no less than about 5–10% of the mRNA in liver cells is expressed with a strong circadian modulation—each with its own specific circadian acrophase. It has been proposed that this pattern of alternatingly peaking biochemical processes may

serve to allow for the temporal segregation of biochemically incompatible processes, that would not be possible to occur simultaneously within one single cell.[2] The concept of temporal segregation promoting optimal function can be extended from single-cell processes to physiological processes affecting the whole organism. There is strong evidence of a circadian modulation of the systemic toxicity of many drugs (e.g. [14,15]). As a consequence, a second plausible hypothesis is that a sustained regular 24-h input pattern will promote optimal function of the organism, whereas a small-amplitude and/or irregular zeitgeber input pattern may negatively affect health and well-being.

Below, some examples will be given of consequences of non-24-h zeitgeber input profiles for rhythm expression and for functioning of the organism. Of relevance are those internal and external zeitgeber-stimuli that impinge on either or both the central and peripheral oscillators, including light, melatonin, activity (and related feeding), temperature and corticosteroids.

Consequences of non-24-h zeitgeber input profiles for rhythms and function

A first way, in which the zeitgeber input can lack a clear and repeated 24-h profile, is when there is *an attenuated or even complete lack of zeitgeber modulation*. A schematic picture of this situation is given in Figure 2, panel B. A few examples on possible consequences are given below.

Rats exposed to *constant dim light for many days* are at high risk to develop internal desynchronization between locomotor, sleep, body temperature, drinking and melatonin rhythms.[16,17] González and Aston-Jones[18] were the first to experimentally study the sleep–wake rhythm of rats placed in *constant darkness for a prolonged period of many weeks*. Due to a prolonged and complete lack of light the amount of wakefulness during the active period decreased, the amplitude of the sleep–wake rhythm decreased and the acrophases of sleep and of wakefulness developed a different phase-relation. The study of González and Aston-Jones also provided an exciting new insight in the *functional* consequences of a chronic lack of light: a dramatic reduction in the noradrenergic innervation of the frontal cortex was demonstrated. Thus, chronic light deprivation may well affect noradrenelin-dependent prefrontal function. This finding is of specific interest to aging, which is already associated with attenuated noradrenergic function: it is conceivable that this attenuation is more pronounced in elderly who lack a clear daily exposure to bright light.

The best example of the consequences of a continuous *lack of light entrainment* in humans occurs in people with complete ocular blindness. This condition can result in a free-running rhythm of, e.g. melatonin secretion, and has strong adverse functional consequences, as indicated by severe sleep complaints and daytime fatigue (e.g. [19,20]). A more subtle effect of chronically attenuated level of light exposure on the expression of circadian rhythms in humans is the association between a lack of daylight exposure and an attenuated amplitude in the rhythm of melatonin secretion.[21] This is a reversible consequence, since both in healthy subjects[22–24] and in poorly sleeping elderly,[21] bright light treatment during the day enhances melatonin release during the night.

Animal studies suggest that the circadian system becomes increasingly sensitive to a lack of light input with advancing age. For example, increasing the daytime light intensity restores the vasopressin deficit in the SCN of old rats[25] and enhances the amplitude of their sleep–wake rhythm.[26] Consequences for peripheral clocks have also been shown: mice kept at 100–200 lx instead of 10 lx show improved stability and (re-) synchronization of their metabolic and endocrine rhythms.[27]

Honma and Hiroshige[28] evaluated the effects of *prolonged continuous light exposure* (i.e. absence of darkness) on circadian rhythms in locomotor activity, body temperature and plasma corticosterone. After a first period of about 2 months during which circadian rhythms were preserved, be it free-running, the rhythms then gradually lost their circadian pattern and ultradian fluctuations emerged. This finding indicates that effects of altered light exposure may develop very slowly—a notion that should be kept in mind when evaluating, e.g. clinical studies on light treatment.

The consequences of a lack of entrainment by *melatonin* have been evaluated in rats by Simon et al.[29] They showed that a continuous subcutaneous infusion of melatonin, resulting in a constantly elevated level of melatonin, attenuated the amplitude of the daily rhythms of temperature and heart rate. With respect to the functional relevance for humans, a low melatonin *amplitude* was found to be associated with insomnia complaints in, e.g. adult and elderly subjects[21,30–32] and intensive care patients.[33]

The consequences of a lack of entrainment by *physical activity* have been evaluated in forced bed-rest experiments. After prolonged forced bed-rest, the rectally measured core body temperature rhythm shows an attenuated amplitude and desynchronization with the environmental LD cycle.[34,35]

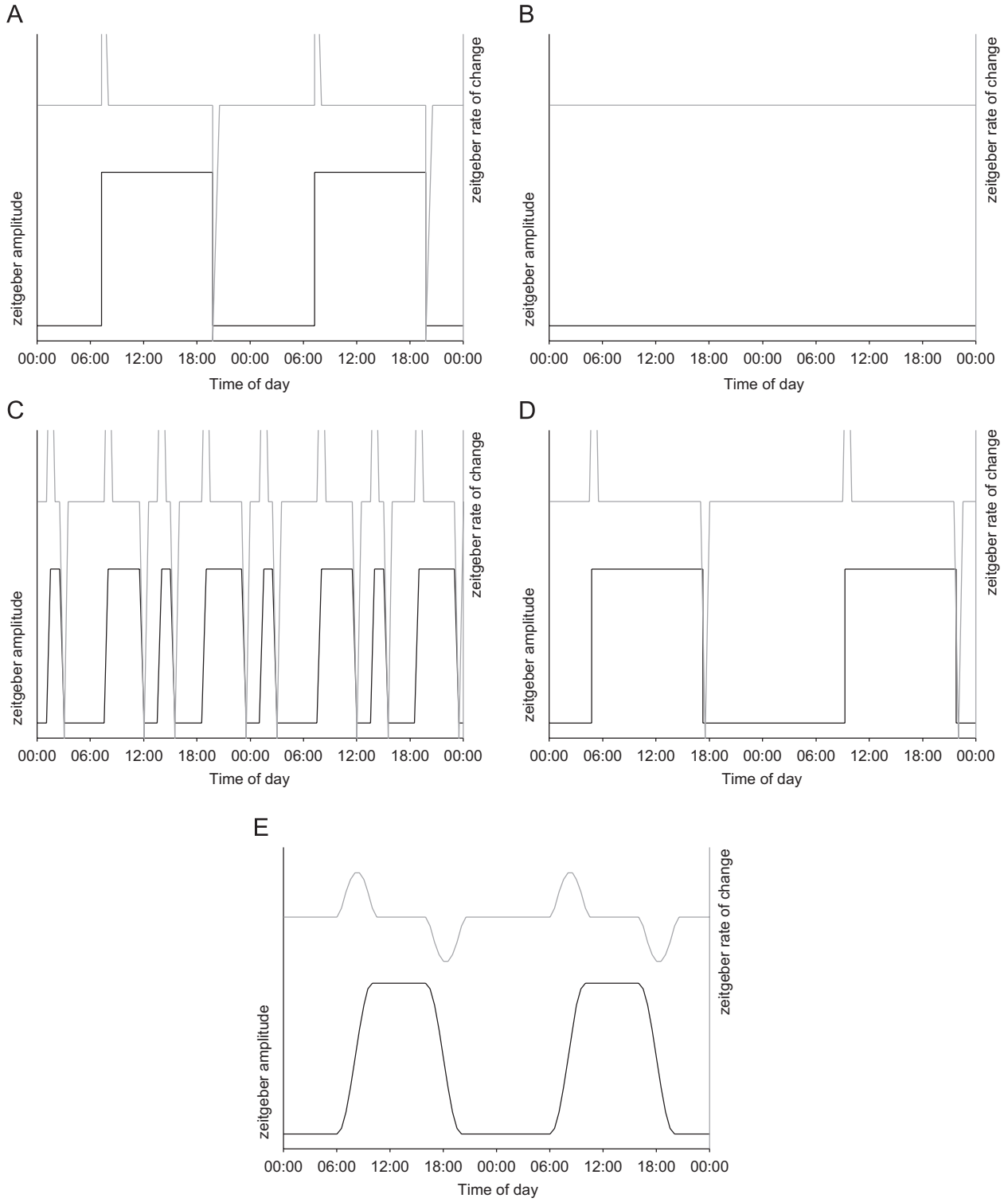

Figure 2 Schematic pictures of double-plotted zeitgeber profiles (black lines) and their first derivative (gray lines). Panel A resembles a typical experimental LD situation. Panel B is a schematic representation of the complete lack of any modulation in a zeitgeber signal. Panel C gives a representation of a quasi-ultradian, fragmented zeitgeber signal. Panel D gives a representation of a zeitgeber signal that shifts in phase from one to the other 24-h period. Finally, panel E represents a zeitgeber signal with a natural onset and offset, in this case modeled after naturally occurring changes in light intensity with dawn and dusk. Note that the first derivative of this natural signal has a considerable area under the curve at the transitions between on and off, whereas the area under the curve at the typical square on–off LD signal of panel A approximates zero. Given enhanced sensitivity to such natural transitions, the circadian timing system may show sensitivity not only to the zeitgeber level itself, but also to its rate of change (i.e. first derivative).

The finding could however not be confirmed for tympanic temperature[36]—where it should be noted that infrared tympanic measurements are prone to error and that tympanic temperature does not always match rectal temperature.[37] It is likely that the effect that a clear rhythm in activity level exerts on the CTS becomes more pronounced in subjects with suboptimal endogenous pacemaker function. In the terminology of the metaphor: a regular push is more crucial for those who do not master the swinging skills too well, or a *weak endogenous oscillator* requires a *strong and regularly timed zeitgeber* in order to accomplish a robust rhythm. Very old subjects and demented elderly are such subjects at risk: it has been shown that a large number of neurons in the SCN become inactive in these conditions.[38,39] Due to the development of actigraphs—miniature activity monitors dedicated to record the typical wrist movement spectrum[40]—the long-term activity monitoring that is necessary to obtain valid sleep and activity rhythm estimates[41] has become feasible for the study of age-related neurodegenerative diseases like Alzheimer's disease, and recently also Parkinson's disease—where more sophisticated devices are needed to discriminate normal movements from tremor.[42–44] Studies that applied these actigraphs showed that the daytime physical activity level is among the best predictors of circadian sleep–wake rhythm maintenance in demented elderly.[45,46] Werth et al.[47] described how the activity rhythm amplitude progressively decreased during the last 598 days of life of a demented patient. Of note, the rhythm showed temporary improvements during periods of 'pacing', which is an intense activity frequently seen in Alzheimer's patients.

The rest–activity rhythm amplitude also has predictive value for health and well-being. A few examples are given. Mormont et al.[48,49] demonstrated in 200 patients with metastatic colorectal cancer that a flat circadian rhythm in physical activity predicted fatigue, appetite loss, nausea, disturbances in physical, emotional, and social functioning, and even mortality. Morgan and Clarke[50] showed that a low level of physical activity increased the risk of insomnia at an 8-year follow up by an odds ratio of about 2. Gehrman and colleagues[51] demonstrated that activity phase abnormalities in demented elderly predicted a shorter survival.

A lack of—or low amplitude—*temperature cycles* would be expected to affect entrainment of both the SCN and peripheral oscillators. We are not aware of experimental studies clamping core body temperature at a fixed level *in vivo*. However, it has been demonstrated *in vitro* that peripheral clocks fail to oscillate if kept at a constant temperature, while they can resume their oscillation if exposed to temperature cycles.[52]

Since *cortisol* could be involved in entrainment of peripheral oscillators, a flattened cortisol rhythm could have consequences for the oscillators and ultimately several functions of the organism. Correlative studies suggest this to be the case. Cortisol normally shows a strong increase before the onset of the major activity period, a crisp peak just after activity onset, and a steady decline thereafter. A decrease in amplitude has been demonstrated in depression,[53] and a loss of the clear early morning peak in the burnout syndrome.[54] It should be noted that the environment in which cortisol is assessed strongly affects it diurnal profile; for example humans measured in a hospital setting show elevated levels respective to their home-assessed levels especially in the evening.[55]

Cortisol rhythms also flatten with aging,[56] although a rhythm remains clearly detectable even in demented elderly subjects.[57,58] One example of the consequences of an attenuated cortisol amplitude has special relevance to cognitive aging. Cain et al.[59] showed that aged hamsters with a small-amplitude cortisol rhythm performed worse on learning tasks than aged hamsters that still showed a clear cortisol rhythm amplitude. Cortisol rhythm amplitude has even been associated with mortality. Metastatic breast cancer patients with a diurnal cortisol profile that remains relatively flat throughout the day show a reduction in natural killer cell counts as well as an earlier predicted mortality.[60]

Since some process associated with *feeding* is strongly implicated in entrainment of peripheral oscillators, it may be proposed that a continuous level of feeding or fasting affects tissue oscillations. Although not much research has yet been published, 'constant starvation' nearly abolishes cyclic gene expression in the liver (see [2]). There is an important and ongoing discussion about the presence of a food-entrainable oscillator not residing in the SCN, on which an excellent review has recently been published.[61]

In summary, correlational and experimental studies support the contention that the lack of a clear and regularly peaking 24-h zeitgeber rhythm is associated with both circadian and functional disturbances, and especially so in the more vulnerable elderly or diseased humans. Phrased according to the terminology of the swing metaphor: those with compromised 'swinging' skills, require a regular and strong push.

A second way in which the zeitgeber input can lack a clear and repeated 24-h profile, is when zeitgeber are present, but show a *quasi-ultradian or fragmented* rather than circadian modulation. This situation is schematically depicted in Figure 2, panel C.

The effects of a prolonged *ultradian pattern of light exposure* have been described in several studies evaluating their masking effects on behavior and physiology (reviewed in[62]). These studies have shown such light patterns to induce ultradian patterns in sleep, body temperature, locomotor activity, feeding and metabolism. Although such patterns have usually been regarded as 'masking'—suggestive of being without functional implications—it is highly likely that they could affect peripheral clocks, which are sensitive to these signals, as discussed above. On the other hand, ultradian light patterns do not induce a strict synchronization of ultradian behavior if such behavior is already present under normal conditions as in the common vole.[62]

A PubMed search did not reveal studies on an enforced *prolonged ultradian exposure to melatonin*. Thus, it does not seem to be known what the consequences of such exposure to central and peripheral oscillators and general functions of the organism might be. Experiments to sort out such effect might be of use: anyone who has assayed human melatonin rhythms may have encountered multi-peaked profiles. There is little doubt on the existence of bimodal melatonin profiles, especially under conditions of long nights and short days[63]; their possible consequences for rhythms and function are however not known.

Several studies have addressed the consequences of a *prolonged ultradian pattern of physical activity*. One intriguing example concerns the common vole, which naturally shows a pronounced ultradian activity pattern. Since the 24-h component of the rest–activity profile—and the concomitant 24-h cycle of feeding and temperature—are presumed to contribute significantly to the synchronization of peripheral clocks, animals with a strong ultradian (relative to circadian) activity rhythm would be predicted to show a reduced circadian amplitude in peripheral clock gene expression. The common vole *Microtus arvalis* is an appropriate model to address this possibility, since it has a very pronounced ultradian behavioral pattern. Using this model, van der Veen et al.[64] indeed demonstrated a nearly constant rather than circadian clock gene expression profile in the liver of the ultradian voles. Although more studies in other species over a range of a predominantly circadian to predominantly ultradian lifestyle are needed to confirm the generalizability of this finding, an experimental follow-up on the finding strongly supports the proposed involvement of a repeated 24-profile of zeitgeber in the induction of a circadian amplitude in peripheral clock gene expression; van der Veen and colleagues showed that forcing these voles into circadian behavioral pattern induced liver cells to express a clear circadian pattern in their clock gene expression as well.[64]

A second example of an ultradian pattern of physical activity concerns aging. During normal aging, the rest–activity profile typically shows a gradual increase in ultradian variability at the cost of a decline in the 24-h component. This pattern has been demonstrated not only in rodents, but also in humans[65] as well as in non-human primates under both normal and accelerated aging conditions.[66] Younger subjects typically show a single extended major period of activity alternating with a single major period of rest, each confined to its own specific phase of the circadian cycle. With aging, this pattern gradually changes into one of multiple transitions between shorter periods of rest and activity, such that both occur throughout the circadian cycle. A simple nonparametric mathematical tool has been developed to quantify the ultradian component in the activity rhythm in a variable called 'intradaily variability'.[67,68] Of note, this variable appears to be much more sensitive than other parameters to age-related changes in the circadian organization of the activity rhythm in both humans and non-human primates.[65,66] Two examples of activity recordings, one with a predominantly circadian profile and one with a predominantly ultradian profile, are given in Figure 3. Does such fragmented rather than circadian pattern of activity, and the consequent presumed attenuated synchronizing effect on oscillators affect functions of the organism? Once more this seems to be the case especially in subjects with a compromised SCN function; demented elderly subjects show moderate correlations ($r = 0.25$–0.35) between the ultradian fragmentation and several parameters of functional, emotional and social well-being.[68]

Imposing ultradian *temperature cycles* has been reported in two studies, which were however not aimed at a comparison with a condition without such cycles.[69,70]

Numerous studies have shown ultradian cycles in *cortisol* superimposed on the circadian rhythm (e.g. [11]). The ultradian profile is due to the pulsatile secretion of cortisol, which may vary with other physiological parameters and with well-being. For example, Bao et al.[71] showed the

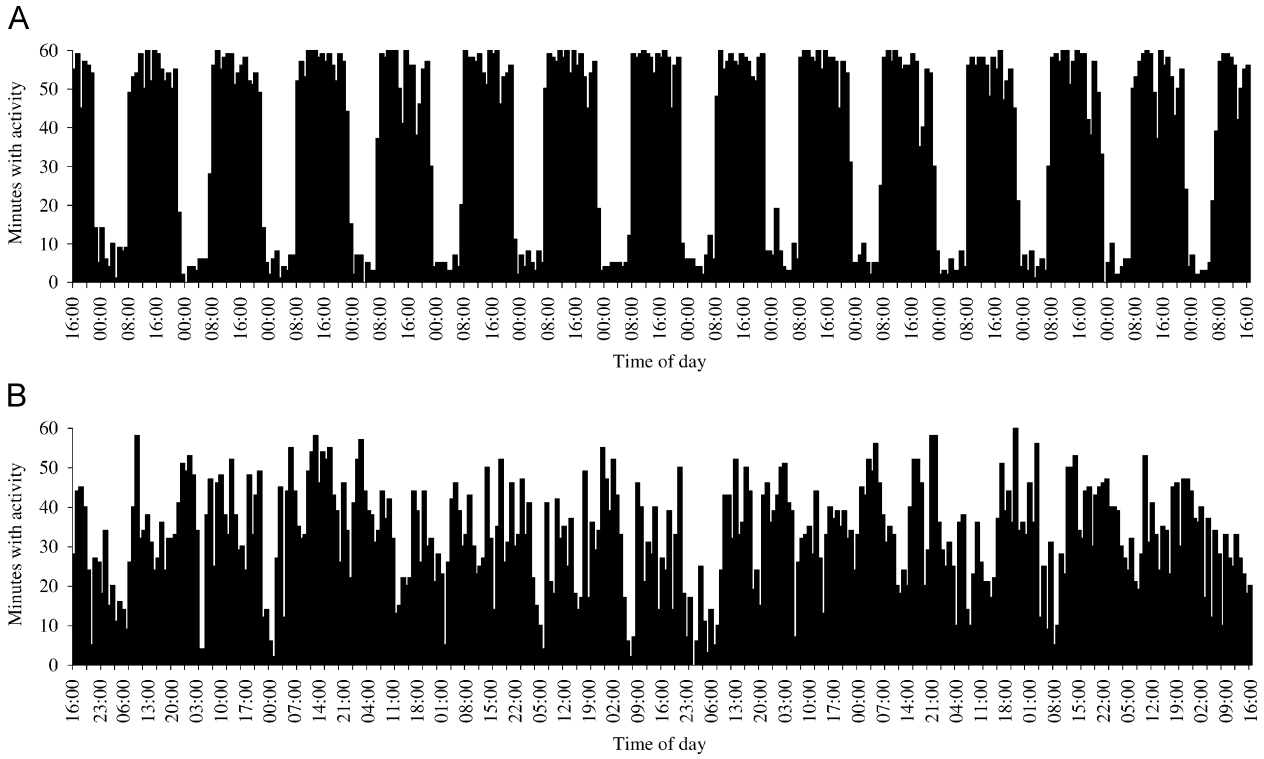

Figure 3 Examples of 14-day activity profiles of two demented elderly subjects. Bins represent the number of minutes with activity for each individual hour. The upper panel shows a subject with a very well-maintained rest–activity rhythm. Note especially the interdaily stability: the 14 individuals daytime profile much resemble each other. The lower panel shows a subject with a virtually complete loss of 24-h rhythmicity. Daily profiles do not resemble each other (Interdaily Stability parameter = 0.10) and the 'spiky' alteration of hours of much activity and little activity represent a strong fragmentation, also known as intradaily variability. Of note, the degree of such fragmentation of the activity pattern shows moderate correlations ($r = 0.25$–0.35) with several parameters of functional, emotional and social well-being (from Carvalho-Bos et al.[68] with permission).

ultradian amplitude to covary with the menstrual cycle. There may be clinical value of the ultradian amplitude: male depressed subjects show an increased ultradian variability in cortisol.[72] However, this finding was not confirmed in female depressed patients.[73] The overall cortisol rhythm is relatively intact in moderate Alzheimer's disease, and if disturbances occur, they can be *independent* from disturbances in the activity rhythm.[58] On the other hand, in a study on two age-related neurodegenerative disorders (Parkinson's disease and Alzheimer's disease) the mass of cortisol secreted with each pulse was found to be increased by about two-third.[74] These two results suggest a relative preservation of the circadian cycle, yet with an increased ultradian secretion amplitude. The relevance of these findings for peripheral clock entrainment or function has yet to be elucidated. Studies that *impose* ultradian cortisol cycles could be of help here, but have not yet been reported as far as we know.

In one study mice were exposed to an ultradian *feeding* schedule, which resulted in a moderate dampening of the 24-h activity rhythm.[64] The amplitude in peripheral clock gene expression did not change, but a marked (~5-h) phase advance was documented. The effect of feeding and fasting on circadian clocks either in the SCN or apart from the SCN has developed to an important area of research with high relevance to present society and health, as reviewed e.g. in.[61]

Finally, a third way in which the zeitgeber input can lack a clear and repeated 24-h profile, is when *zeitgeber* are present, but *repeatedly shift in phase*, as in shift work and in frequent flights across time zones. Figure 2D gives a schematic representation of a zeitgeber signal that shifts in phase from one to the other 24-h period. Contrary to the previous two paragraphs the impact of such shifts will not be discussed separately for each zeitgeber, because abrupt phase changes usually occur simultaneously in the profiles of light

exposure, physical activity and feeding. Because the profiles in melatonin, temperature and cortisol resynchronize only after some cycles, phase shifts induce a temporary desynchronization of central and peripheral rhythms within the organism (reviewed in [75]). Repeated exposure to such desynchronization has strong repercussions for health. Of the numerous studies that addressed the health consequences, only a few examples will be given here.

As to animal studies, a first example of the importance of a stable 24-h profile is given by the correlational studies of Satinoff and colleagues.[76,77] They show that the day-to-day stability of the core body temperature profile is associated with sleep quality in old rats. Froy et al.[78] showed that transgenic mice with very pronounced and synchronized circadian amplitudes also show an extended life span. A recent study by Conti et al.[79] suggests that the pronounced reduction of the core body temperature during the inactive period could contribute to the life span of the animal. It remains to be investigated whether individual differences in the trough of the temperature rhythm indeed have predictive value for health. At least some experimental animal studies support the importance of a fixed 24-h profile for health. Chronic circadian desynchronization imposed by a weekly reversal of the LD cycle increased the mortality of hamsters with cardiomyopathic heart disease.[80] Also in aged mice, chronic jet-lag increases mortality.[81]

Studies in humans confirm the animal findings. The impact of shift work and jet lag on health and well-being has been studied and reviewed extensively. A present focus of interest are individual differences, of which aging is one important factor (e.g. [82,83]). Cho et al.[84,85] give a strong example of the functional consequences of extreme occupational phase irregularity. They demonstrated that airline cabin crew who frequently traveled across time zones for several years suffered from increased cortisol levels, cognitive deficits and temporal lobe atrophy. None of these disturbances were present in a control group of crew with the same job demands, but traveling on the North–South axis and thus not exposed to shifts in the LD cycle.

The phase shifts do not have to be so extreme as is the case in shift work or jet-lag in order to affect the function of the organism. In a correlational study, Fukuda et al.[86] showed that an irregular lifestyle was associated with a delayed early morning rise in core body temperature. Carvalho-Bos et al.[68] investigated the relation between activity rhythms and a number of functional measures in 87 demented elderly, and found that the day-to-day stability of the activity profile was an even better predictor of cognitive and mood disturbances than, e.g. nocturnal restlessness *per se*. Experimental studies confirm a causal role of irregular lifestyle on well-being. For example, forced increased irregularity of the sleep–wake cycle increases daytime sleepiness.[87]

A final observation with respect to the importance for health of adherence to the 24-h rhythm that has been present throughout the evolution of the organism, is that it seems to be equally important to adhere to the 1-year-periodic *seasonal* rhythm that has been equally present throughout evolution, and is in mammals also integrated in the SCN. If animals are put on a seasonal rhythm of longer and shorter days with a period of less than a year, this does not only induce a decreased SCN-function,[88] but also an acceleration of age-related physiological changes, dysfunctions, and ultimately death.[66]

The examples above by no means represent a comprehensive review of all relevant studies—which has not been the aim of the present paper. They do suggest however that prolonged exposure to unusual zeitgeber patterns—be it a lack of circadian modulation, an ultradian pattern, or a non-24 h pattern—could have strong implications for clock functions and the consequent health condition of the organism. This should be kept in mind in evaluating results from studies that apply constant routine, ultrashort sleep–wake cycle, and forced desynchrony. It may well be that some of the results from these studies do not fully represent all normal clock mechanisms and interactions as they are present under the normal 24-h environmental cycle to which we have evolutionary adapted.

Aging: increased sensitivity to low-amplitude, ultradian or irregular zeitgeber profiles?

In several of the examples given above, the consequences of a low-amplitude, ultradian or irregular zeitgeber pattern seem more pronounced in elderly subjects. We propose that this is the case because the complex system of central and peripheral oscillators in elderly subjects may have less 'reserve'. In the terminology of the swing metaphor, elderly may get to resemble the young kids who do not master the necessary movements well enough to keep the swing going. A more appropriate metaphor would be that elderly gradually loose the ability to smoothly make the leg movements necessary to keep the swing going. As outlined in the Introduction, it is likely that the

disturbing effect of inadequate environmental stimulation on the CTS worsens if the robustness of the endogenous circadian oscillations weakens.

There is indeed some support for oscillator changes in old age. Concerning the central pacemaker, it is known already for some time that vasopressin expression in the human SCN decreases at old age—and even earlier in demented elderly subjects.[38,39] Already earlier in the process of aging, a decrease in the day–night amplitude of vasopressin expression occurs.[89]

Concerning peripheral oscillators, one human postmortem study showed a loss of the circadian expression in clock genes in the pineal in demented elderly.[90] Yamazaki et al.[91] studied the effect of aging on central and peripheral clocks in transgenic rats and investigated whether age-related changes in circadian organization relate to changes in the central pacemaker, to changes in the peripheral slave oscillators, or to changes in their coupling mechanisms. By measuring Per1-luc oscillations in SCN and peripheral tissue taken from young and aged transgenic rats, they demonstrated that old rats preserved their rhythms in the SCN and some peripheral tissues, whereas rhythmicity in other tissues was either absent or phase advanced relative to the light cycle. Because rhythms were still inducible in those tissues that were arrhythmic Yamazaki and colleagues concluded that these tissues retained the capacity to oscillate but might not have been driven appropriately *in vivo*. It may thus be that a *stronger* drive is necessary in order to maintain a coherently synchronized complex of oscillators.

Observations on rhythms in demented elderly subjects support the notion by Yamazaki et al. of a dissociation of downstream rhythms. Thus, disturbances in the rhythms of activity and cortisol may occur independently,[58] as well as phase-changes in activity and core body temperature.[92] The findings of age- and dementia-related changes in the central and peripheral clocks are complemented by numerous reports on a decrease in the circadian amplitudes of multiple physiological and behavioral variables (for reviews, see [93–95]). In addition, ultradian components in the activity rhythm become more pronounced.[65,66] Overall, these results indicate that aging affects oscillations in some but not in all tissues, may act on interactions among circadian oscillators, and may attenuate the ability of the SCN to drive damped downstream oscillators.

Would elderly humans be aware of their less robust endogenous system of oscillators? Several studies suggest that there may at least be an implicit recognition of this, and of a compensatory adherence to a stricter 24-h zeitgeber pattern than younger subjects do. As recognized firstly by Minors (e.g. [96,97]) and by Monk (e.g. [98,99]) elderly show a much reduced within-subject day-by-day variability in their mealtimes,[96,97] lifestyle[99] and social behavior.[100,101] In one study this even resulted in an increased activity rhythm amplitude in elderly subjects as compared to younger subjects.[102] The increased regularity of behavior of elderly has been interpreted as a possible compensation for the vulnerability of their CTS. Indeed, older people have more trouble coping with shift work and jet lag.[103] Monk has therefore proposed that the adherence to regularity is an unconscious adaptive response that promotes a more coherent set of zeitgebers and consequently a more tightly entrained circadian system. Support for this connotation comes from the observation that elderly subjects with higher levels of lifestyle regularity report fewer sleep problems[100,101] and a more pronounced nocturnal body temperature trough,[101] both suggesting a better functioning CTS. Whether or not elderly humans are consciously aware of a less robust endogenous system of oscillators, the examples given in the present paper suggest that the (experimental) *induction* of regular zeitgeber might support the central clock, the downstream oscillators, and their coupling, and could thus promote optimal function and health. The next paragraph gives examples in support of this contention.

Enhancing regular 24-h zeitgeber input profiles

If regularity of zeitgeber supports synchronization of central and peripheral clocks, measures that enhance regularity would be predicted to support the function of the CTS and consequently of the physiology and behavior of the organism.

Regular light

Many studies have shown that an increase in light exposure gradually improves function in a number of clinical conditions. For example, seasonal affective disorder improves after about a week of daily light exposure, usually 2500 lx for 2 h or 10.000 lx for half an hour.[104–106] A second disorder, in which light treatment is of use, is Alzheimer's disease. Here, improvement of the sleep–wake rhythm and function has been demonstrated both with 2 h of daily light exposure[107–109] and with whole-day bright light, given for several weeks,[110]

which support the notion of preserved neuronal plasticity even in old brains as affected as by Alzheimer's disease.[111] We propose that one of the mechanisms involved in the efficacy of whole-day bright light might be that it provides a stable high-level light intensity background instead of incidental irregular light pulses that could have the adverse effect of shifting up and down the rhythm phases of the often light-deprived institutionalized demented elderly. Furthermore, subjects with the most severely disturbed rhythms show the most pronounced responses to light treatment.[112] Light exposure also improves function and well-being in elderly insomniacs (e.g. [113]) and in healthy elderly subjects (e.g. [94,114]). Of note, suboptimal function of the CTS has been proposed in all these conditions. In terms of the swing metaphor, a regular push appears advantageous especially for those who for some reason do not optimally master the optimal leg movements anymore to keep the oscillation going.

Of importance, the fact that clinical improvement is usually *not* correlated with specific *phase*-shifts (e.g. [115]) should not be interpreted as evidence against involvement of the CTS. It is here proposed that the light treatment might enhance optimal synchronization between oscillators, and that this process may not simply surface acutely in changes in the phase of e.g. temperature or melatonin profiles. For example, light treatment has been shown to enhance nocturnal melatonin secretion in insomniacs,[21] indicating an increased amplitude in one of the outputs of the CTS.

There are some indications that the regularity of light *onset* may support the function of the circadian timing more than the regularity of light *offset* does. Rosenwasser et al.[116] compared the entraining properties of a regular LD cycle with those of skeleton photoperiods, i.e. brief pulses only at dawn, dusk or both. The dawn signal appeared to be sufficient for entrainment. Comas et al.[117] showed in mice that the first hour of light exposure has the most pronounced effect on the clock; further hours of light exposure continue to affect the clock, but somewhat less pronounced. Comas et al. suggested the enhanced effect of the first hour after lights off could be due to adaptation mechanisms. Indeed, the response of the human CTS to light exposure is most pronounced if the light pulse follows a period without exposure.[118] Such mechanism might also underlie the finding that bright light treatment for seasonal affective disorder is more effective when given in the morning as compared to the evening.[119,120] Thus, it appears that the clock is not only sensitive to the light level, but also to its rate of change, i.e. the first derivative of the light exposure signal.

With respect to the light-onset rate of change, some observations suggest that an evolutionary natural appearance of the zeitgeber may be most effective. Boulos and Macchi[121] showed in Syrian hamsters that the addition of simulated twilights—instead of the regular 'square' light onset—to LD-cycles reduced the day-to-day variability in activity onset. As is schematically shown in Figure 2E, such gradual increase in light intensity at dawn strongly affects the shape of the first derivative of the light exposure signal. Whereas the first derivative of a square lights on/off schedule is theoretically of zero duration and no area under the curve (Figure 2A), the normal sinusoid lights on/off signal induces a first derivative profile with longer onset and offset deflections and a clear area under the curve (Figure 2E). We propose this difference to underlie the reported increased sensitivity of the CTS to natural dawn- and dusk-like zeitgeber onsets and offsets. A clinical study indeed suggests that a regular natural light onset signal may be favorable even at lower intensities than the 2500–10,000 lx that has often been assumed to be the minimal effective 'dose' in light-therapy. In demented elderly, the mere simulation of dawn light exposure improved their often disturbed sleep–wake rhythms.[122] A final observation on the application of a regular light regime is that whole day exposure to light of about 1000 lx also favorably affects sleep–wake rhythms in demented elderly, even if the exposure is given repeatedly only during the time of day traditionally seen as a 'dead zone', i.e. not affecting the phase of the CTS.[110]

Regular melatonin supplementation

There is extensive support for the efficacy of melatonin to resynchronize the sleep–wake rhythm in blind people, as well as in shift-work and jet-lag (reviewed in [3]), and recently also in children with probable suboptimal function of the CTS.[123,124] In rats, desynchronization caused by the absence of a 24-h rhythm in environmental light could be attenuated by supporting the endogenous circadian oscillation by daily melatonin administration at a fixed time (e.g. [125]). As far as we are aware only one group has addressed the importance of a *fixed* timing of melatonin prescription in humans. Kunz and coworkers[126,127] even suggested that a prescription that might result in varying administration times (e.g. ''at bedtime'') could harm

clock synchronization and lead to adverse effects. They also pointed out that the synchronizing effects could evolve slowly over time. There is a paucity of human data on the possibility that the effect of melatonin supplementation differs depending on whether it is given only once or repeatedly at the same time of day, everyday. In a controlled ambulatory study in men with untreated essential hypertension, Scheer et al.[128] demonstrated that *repeated* (daily for 3 weeks) but not *acute* (one night) oral melatonin (2.5 mg) intake 1 h before sleep reduced systolic and diastolic blood pressure during sleep by 6 and 4 mmHg, respectively. As a consequence, day–night amplitudes of the rhythms in systolic and diastolic blood pressure were increased by 15% and 25%, respectively. Repeated (but not acute) melatonin also improved sleep. Since the improvements in blood pressure and sleep were statistically unrelated, sleep improvements could not account for the reduction in nocturnal blood pressure. It is therefore more likely that subjects differ in their relative sensitivity of sleep- and blood pressure regulating systems, downstream from the central oscillator in the SCN. Animal studies support positive health consequences of prolonged regular melatonin intake. Armstrong and Redman[129] have reviewed studies that suggest that the daily supplementation of melatonin increases the life span of animals, and concluded that the induction of a strong circadian amplitude could be the most likely mediating mechanism.

Finally, the possibility should be kept open that not only a regular melatonin *onset*, but also a regular and crisp melatonin *offset* may support the CTS. Because the melatonin secretion can directly be suppressed by exposure to bright light, the favorable effects of regular early morning light exposure described above might in part be brought about by its induction of a regular and crisp early morning melatonin offset.

Regular rest–activity cycles and exercise

A common advice for optimal sleep–wake rhythm regulation is to adhere to a regular sleep schedule, and especially to a regular get up time, i.e. activity onset time. Of note, sleep offset is indeed more strongly correlated with various circadian phase markers than sleep onset.[130] A recent observation in rats indicates that even a mild sleep deprivation induces a reduction of about 40% in the SCN neuronal activity.[131] This finding makes it likely that shortcuts on the sleep period, frequently occurring in our present 24-h society, could attenuate the circadian amplitude of the major electrical activity output signal of the SCN. Indirect support comes from a controlled experimental study in young adults, where regularization of sleep–wake schedules for 4 weeks led to strong and long-lasting improvements in daytime alertness and nocturnal sleep efficiency.[132] However, in an older study, sleep was not sensitive to regularization—perhaps indicating a ceiling effect due to good sleep in young adults.[133] A circadian effect was still likely in the latter study, because the core body temperature rhythm amplitude became more pronounced.

Even more prominent effects on the CTS might be expected with intense physical activity, i.e. exercise (reviewed e.g. in[134]). Regular exercise facilitates entrainment to an abnormal 23:40 h day–night period.[135] The efficacy of regular exercise to re-entrain after a phase shift is equivocal (reviewed in[136]). There is some indirect support for a stronger effect of prolonged regular exercise as compared to acute physical exercise on one of the most visible circadian regulated functions: sleep and wakefulness (reviewed e.g. in[137]). Epidemiological studies indicate that especially prolonged and regular exercise is associated with better nocturnal sleep and less daytime tiredness.[138,139] As can be concluded from meta-analyses, experimental studies suggest a causality in this relation: especially in subjects with suboptimal sleep[140,141] or general health (e.g.[142]). Also in rodent studies, the strongest entraining effects of exercise are found when other time cues are absent, i.e. when the CTS functions suboptimally.[143,144] Of importance for the proposed increase in relevance of regularly repeated zeitgeber because of a less robust endogenous circadian system in old age, prolonged regular exercise in elderly subjects also normalized the typical age-related fragmentation of rest–activity rhythms into quasi-ultradian bouts of rest and activity.[145] Werth et al.[47] followed the rest–activity rhythm of a demented patient during his last years of life, and noted temporary rhythm amplitude increases associated with periods of increased daytime activity that are known as 'pacing'.

The effect of exercise on sleep may develop only slowly. For example, sleep improvement was found after 16 weeks—but not 8 weeks—of regular exercise in elderly subjects with sleep complaints.[146] Although a comparison between different studies is cumbersome, it is noteworthy that in contrast to the objective sleep–wake rhythm improvement after 3 months of exercise,[145] a 2-week period of daily exercise in elderly subjects

improved only their subjective sleep experience, but not their objective sleep.[147] A rat study on the effect of exercise on obesity induced by frequent phase shifts likewise found a significant body-weight controlling effect of regular exercise only after 3 months.[148] Finally, regular exercise has functional consequences that reach as far as cognitive function. For example, regular exercise in sedentary elderly subjects improves performance on executive control tasks[149] and prefrontal activation.[150] Given the importance of sleep for brain plasticity and cognition (e.g. [151,152]), it would be of interest to investigate to what extent exercise-induced performance improvements are mediated by exercise-induced improvements of sleep and the sleep–wake rhythm.

Regular temperature pulses

Although there is strong evidence for the effects of single temperature pulse on the animal and human CTS (reviewed in[5]), as well as for the synchronizing effect of induced temperature cycles on ectotherms (reviewed in[153]) and on peripheral clocks (e.g. [52]), there is a virtual lack of studies investigating the effect of a repeated, regular temperature pulse in humans. The possibility should be kept open that temperature changes may contribute indirectly to the effects of regular light pulses, melatonin, rest–activity cycles and exercise on the CTS, because all these zeitgeber signals also affect body temperature. Under normal everyday life conditions, the core body temperature rhythm is amplified as compared to constant routine laboratory conditions.[10,154] A new perspective on the effects of body temperature on brain areas involved in circadian and sleep regulation, is that these areas may be more sensitive to changes in skin temperature than to changes in local brain (core) temperature,[5,69,70,155] and that abnormalities in skin temperature regulation could thus contribute in circadian and sleep disturbances.[156,157] Because the circadian amplitude in skin temperature can be amplified to one of several degrees Celcius through changes in body position and sleep behavior,[9,10,154] regularity in the latter behaviors would enhance this tentative zeitgeber signal. Finally, it should be noted that the core body temperature increases with intense light and physical activity, and decreases with a supine position (as during bed rest) and melatonin. The effect of light on core body temperature depends on whether the species is nocturnal (as rats) or diurnal (as humans) and is primarily, though not exclusively, mediated by the SCN.[158] The effect of melatonin on core body temperature is due to an increase in heat loss resulting from a selective increase in distal skin (but not cerebral) blood flow.[159] Thus, a regular active day with a regular LD exposure secondarily also enhances the regularity in the body temperature rhythm.

Regular cortisol

Given that glucocorticoids have been considered to play a key role in the blood-borne signaling pathway involved in peripheral clock synchronization, it would be of interest to examine the effect of a regular cortisol increase on the CTS. Although we are not aware of experimental studies specifically addressing this issue, some correlational data are available that suggest that the presence or absence of clear and repeated cortisol pulse is associated with human function and health. Cortisol increases just before waking up in the morning, peaks within an hour of awakening and subsequently a declines monotonously over the rest of the 24-h day. The increase in cortisol triggered by waking up is considerable; about 50% within the first 30 min after awakening.[160] Environmental light exposure directly after awakening increases the amplitude of this morning peak.[161] It may thus be hypothesized that a regular crisp cortisol pulse would be promoted by a regular get-up time, regular early morning light exposure. Moreover regular food intake and exercise could similarly promote a clear cortisol rhythm.

Regular feeding

Although there has been considerable interest in health and the frequency of meal times (e.g. [162,163]), a PubMed search did not yield human studies in which experimental induction of a sustained more regular 24-h pattern of food intake has been applied and evaluated. On the other hand, irregular meal times in association with shift work have been noted to affect gut function.[162] It has been proposed that the reduced within-subject day-by-day variability in mealtimes that many elderly show,[96,97] are part of a compensatory response to cope with a less robust CTS. Indeed, a group of successfully aging elderly followed up over 4 years showed an increased regularity of food intake.[164] It is likely that regular feeding could affect the CTS also through its effects on cortisol and body temperature changes due to diet-induced thermogenesis.

Other possible inputs to the CTS

Three other possible inputs to the CTS deserve to be mentioned briefly. First, social interaction might act as a zeitgeber.[165] It might however be difficult to discriminate social interaction from the usually associated stimuli including light, activity, posture and arousal level. Second, the vigilance states of non-REM sleep, REM sleep and wakefulness—partly controlled by the SCN—alter the electrical activity of SCN-neurons.[166] Thus, regular sleep–wake cycles and regular within-sleep sleep-stage cycles might contribute to a robust rhythm in SCN electrical activity. Finally, placebo-controlled studies indicate that long-term repeated indirect stimulation of the brain by means of transcutaneous electrical nerve stimulation (TENS) at a fixed time of day improves activity rhythms—once more most convincingly in demented elderly with suboptimal function of the CTS.[167–169]

A possible mechanism underlying slowly developing effects of regular zeitgebers

Finally, we would like to briefly discuss a possible neuronal network mechanism involved in the differential sensitivity of the CTS to a single zeitgeber versus zeitgebers repeated regularly with a 24-h interval. We propose the mechanism to be similar to the mechanism that is responsible for the observation first described by Holloway and Wansley, i.e. that the retrieval of a previously learned task is optimal after 24 h and multiples of 24 h, and suboptimal during the intervals in-between.[170] This finding has been replicated repeatedly and depends on an intact SCN. It can be interpreted in terms of the well-known 'state-dependency' theory, where 'state' now indicates the circadian phase when learning took place. From this perspective, the state of the neuronal network involved in—and modified during—the newly learned task shows the highest similarity to the state it was in during the first exposure to the task at multiples of 24 h. Although this concept has been applied to SCN—involvement in structures with a specific role in learning, e.g. the hippocampus, the learning rule might as well apply to the neuronal networks of the CTS, including the SCN itself.[171] Thus, a zeitgeber pulse that repeats itself after a period of 24 h does not impinge on a 'naive' neuronal network, but on a neuronal network that is in a state that resembles the state induced by the previous zeitgeber pulse, 24 h before. Therefore, slowly developing changes to be induced in the network by repeated exposure to the zeitgeber, like the coupling of individual oscillators and sub-networks (e.g. [172–174]), would most effectively be induced if the very same zeitgeber pulse hits the network again at the time when the network is closest to the 'desired' state, i.e. at regular 24-h intervals.

In case a certain state is reached, continuation of the regular repeated zeitgeber exposure might prevent the network to drift away from this state, as could, e.g. result from a decreasing coupling strength between individual oscillators and sub-networks. The hypothesis put forward here thus argues against a 'dead zone', i.e. a circadian phase during which the SCN would not be responsive to zeitgeber at all. Whereas a dead zone might appear to be present in response to a single zeitgeber pulse, the system would be predicted to respond differently depending on whether a zeitgeber is repeatedly and regularly present during the 'dead zone' phase or completely lacking for a prolonged time. Once more returning to the swing metaphor, even a small push can keep a child swinging, as long as it's given repeatedly and regularly with an exact time interval.

Practice points

1. There is more to the entrainment of the CTS than is determined by the momentary exposure to stimuli that act upon it and its phase-dependent sensitivity to these so-called 'zeitgeber'.
2. A *continued absence, day-by-day irregularity* and *fragmentation* of the 'zeitgeber' may affect the CTS as well. Although the review gives some possibilities, including peripheral clock desynchronization, the mechanisms underlying the effects of (ir)-regularity are unknown; yet, irregular zeitgeber rhythms no doubt have adverse consequences for health.
3. The more someone is at risk of a suboptimal functioning CTS, as in old age, dementia and insomnia, the more the CTS may become dependent on regular zeitgeber, and the more they may profit from an imposed regular 24-h pattern of zeitgeber including light exposure, physical activity and bedtimes.
4. Effects of imposed regularity of zeitgeber exposure on the CTS and on health may develop slowly—in sharp contrast to, e.g. immediate phase shifting effects of single zeitgeber pulses.

Research agenda

Future research on the effects of zeitgeber on the circadian system should:

1. Also include evaluations of effects and mechanisms of irregular zeitgeber exposure.
2. Be aware that effects of (ir)regularity may develop slowly.

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