

Opinion

Circadian-Time Sickness: Time-of-Day Cue-Conflicts Directly Affect Health

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A daily rhythm that is not in synchrony with the environmental light–dark cycle (as in jetlag and shift work) is known to affect mood and health through an as yet unresolved neural mechanism. Here, we combine Bayesian probabilistic ‘cue-conflict’ theory with known physiology of the biological clock of the brain, entailing the insight that, for a functional pacemaker, it is sufficient to have two interacting units (reflecting environmental and internal time-of-day cues), without the need for an extra homuncular directing unit. Unnatural light–dark cycles cause a time-of-day cue-conflict that is reflected by a desynchronization between the ventral (environmental) and dorsal (internal) pacemaking signals of the pacemaker. We argue that this desynchronization, in-and-of-itself, produces health issues that we designate as ‘circadian-time sickness’, analogous to ‘motion sickness’.

Why Does Circadian Rhythmicity Affect Health?

A vital task of the biological clock of the brain is to pace physiological processes in a circadian rhythm that is synchronized with the environmental light–dark cycle. This allows for anticipation of time-of-day-dependent demand on resources involved in, for instance, sensory alertness, physical activity, and the immune system [1,2]. Circadian pacing that is insufficiently synchronized with the environmental light–dark cycle (as in jetlag or shift work) is known to disturb mood, well-being, and health [3,4].

Although disrupted sleep can be a major contributor to such problems [5], recent work demonstrates that a disrupted light–dark cycle by itself can exert a direct influence on mood and well-being without affecting sleep duration [6,7]. Recently, a relatively large study even concluded that sustained intraday and interday variability in circadian behavioral activity rhythms, but not in sleep duration and sleep onset latency, predicts mortality in older humans [8]. As such, a good understanding of circadian rhythmicity in the pacing of the brain can be important for many individuals in our 24/7 society. Although it may seem obvious that a desynchronization in the functioning of organs throughout the body is a compromising factor for health [9], a mechanistic and functional understanding of such desynchronization is still lacking.

In this Opinion, we ask whether we can advance such understanding from a normative computational perspective. We contemplate that, theoretically speaking, the inference by the brain of time-of-day can be regarded like a perceptual process. Sensory perception involves the **cue-combination** (see [Glossary](#)) of perceptual **cues**, each having its own intrinsic noise and likelihood, which may vary over the day. Inference of time-of-day involves a combination of internal and environmental time-of-day (Zeitgeber) cues [10]. Perceptual cues can occasionally

Trends

Recent work shows that a disrupted light–dark cycle in itself can exert a direct influence on health without affecting sleep duration.

Sustained variability in circadian behavioral activity rhythms, but not in sleep duration and sleep onset latency, appears to be predictive for mortality in older humans.

There is no mechanistic or functional explanation for these recent findings.

The brain can be regarded as an inference engine optimizing probabilistic models of what caused its input, providing a normative explanation.

Similar to motion sickness (which is induced by perceptual conflicts in internal and environmental motion cues), conflicts between internal and environmental time-of-day cues can directly compromise health: circadian-time sickness.

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be in conflict; an illustrative case of such **cue-conflict** is motion sickness, where the vestibularly sensed motion (reflecting internal motion) and visually sensed motion (reflecting environmental motion) insufficiently match. Perceptual cue-conflicts can be resolved by remapping prior expectation about the sensory signals (e.g., when getting used to new spectacles [11]). Time-of-day cues can also be in conflict occasionally, particularly after a trans-meridian flight or after transitions involving daylight saving time.

Engineer's Approach

How would an engineer design an optimal pacemaker that depends on a multitude of time-specifying signals, each signal having an individual reliability that may vary over the day? A conventional approach to combine multiple sources of probabilistic information optimally is **Bayesian inference** [12], which provides an optimal way to combine prior stored time-of-day information with the likelihood of environmental time-of-day cues.

It is now increasingly accepted that the brain is an inference engine based upon optimizing probabilistic models of what caused the sensory input [12]. Key to this idea is a probabilistic brain that is able to generate predictions against which sensory input is compared to update prior assumptions. Related to our particular case of cue-combination, Bayesian inference has been

Box 1. A Probabilistic Theory for Circadian Pacemaking

In Bayesian models, a generic inference is decomposed, first, into a 'likelihood' probability distribution [the probability for the cues (C), given a property, sometimes called 'hidden state', of the environment (T), denoted by $P(C|T)$], and second into, what is called, a 'prior' [the *a priori* expected probability related to the property of the environment $P(T)$]. Likelihood and prior are combined to produce the 'posterior' probability $P(T|C)$, representing the probability for a particular property of the environment (T), given the cues (C), and is obtained from Bayes' rule with general form (Equation I)

$$P(T|C) \propto P(C|T)P(T) \quad [I]$$

The prior constraint $P(T)$ can be associated with the time indicated by an internal master pacemaker. This prior is described by a Gaussian probability distribution centered on the internal pacemaker time (t_{int}) with spread σ_{int} (depending on the moment of the day; Equation II):

$$P[t; t_{int}, \sigma_{int}(t)] = \frac{1}{\sqrt{2\pi}\sigma_{int}(t)} \exp\left[-\frac{(t-t_{int})^2}{2[\sigma_{int}(t)]^2}\right] \quad [II]$$

The likelihood probability distribution can be associated with the circadian time provided by an external source (t_{ext}), centered on the environmental time (Equation III):

$$P[t; t_{ext}, \sigma_{ext}(t)] = \frac{1}{\sqrt{2\pi}\sigma_{ext}(t)} \exp\left[-\frac{(t-t_{ext})^2}{2[\sigma_{ext}(t)]^2}\right] \quad [III]$$

The total probability (area under each Gauss distribution) sums to unity. Note that this probability distribution is shifted in time relative to the distribution associated with the internal 'prior' time whenever the time specified by the external source (t_{ext}) is different from the internal pacemaker time (t_{int}).

The likelihood and prior distributions are being combined to produce a posterior estimation according to Bayes' rule (Equation IV):

$$P[t; t_{int}, t_{ext}, \sigma_{int}(t), \sigma_{ext}(t)] \propto P[t; t_{ext}, \sigma_{ext}(t)]P[t; t_{int}, \sigma_{int}(t)] \quad [IV]$$

Figure 1 illustrates an example of the shapes of each of the above-mentioned Gaussian probability distributions as a function of the time-of-day estimate within the circadian period. The shape parameters of the Gaussian merely serve to illustrate how the relevant signals are being combined; the individual shape parameters have been chosen arbitrarily. In this general example, the probabilities attached to the prior and likelihood differ slightly.

Note that, in this explanation, we only use a single time parameter for the internal signals (t_{int}) and one for the external signals (t_{ext}). However, there can be multiple internal and external signals, together making up one single distribution associated with t_{int} and t_{ext} .

The width of the probability distributions may vary during the day. For example, during dawn and dusk, the external solar illuminance varies predictably, while during mid-day solar illuminance is relatively constant. This implies that during dawn and dusk the probability distribution associated with the likelihood of the time-of-day provided by solar illuminance is highly informative (i.e., relatively peaked). However, at mid-day, it is less informative and relatively flat.

Glossary

Bayesian inference: takes into account the probability of an event, based upon conditions that relate to the event. It comprises a 'likelihood' probability distribution (the probability for the sensed data, given an environmental property) and a 'prior' probability distribution (the *a priori* expected probability for the environmental property). Together, likelihood and prior determine the 'posterior' probability, representing the probability for a particular property of the environment, given the sensed data.

Circadian-time sickness: in analogy to motion sickness, we have coined the term 'circadian-time sickness'. Motion sickness is induced by conflicts between internal and environmental motion cues.

Circadian-time sickness is induced by conflicts between internal and environmental time-of-day cues. Conflicts in time-of-day cues lead to a desynchronization between the ventral and dorsal output of the biological clock, which leads to dysregulation of targets downstream of the biological clock, thereby entailing circadian-time sickness.

Cue: a sensory cue, or in short cue, is a sensory input signal, indicating the state of some environmental property.

Cue-combination: involves the probabilistic combination of multiple cues by the brain to create a single interpretation of an environmental property. Probabilistic cue combination takes into account the variability (or statistical properties) of individual cues. The more reliable a cue is, and the more weight (gain) the cue gets in cue combination.

Cue-conflict: ensues when multiple cues specify conflicting information about an environmental property.

Suprachiasmatic nucleus (SCN): refers to an area in the hypothalamus comprising thousands of coupled individual autonomous cellular oscillators that express genes that cyclically regulate their own expression. Together, the cellular oscillators generate a composite waveform: the ensemble SCN output activity. The SCN comprises two separate compartments with distinct functionality: a ventral and a dorsal subdivision. The ventral SCN exhibits an immediate light responsiveness with a weak autonomous activity,

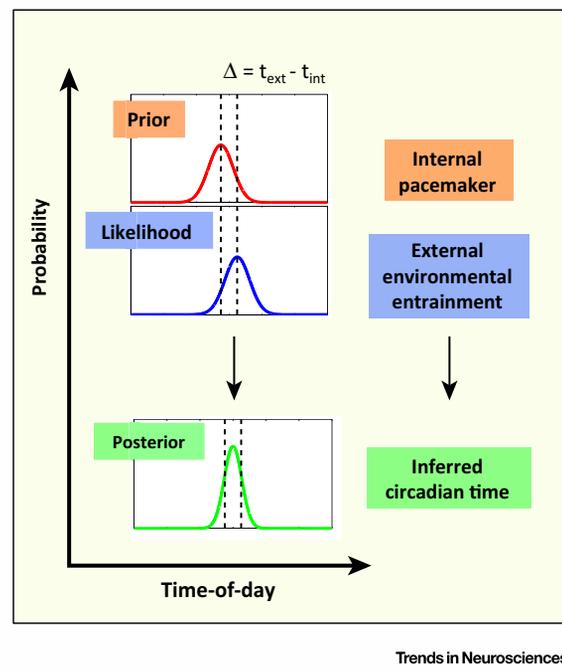


Figure 1. Bayesian Inference of Circadian Time. In a general Bayesian probabilistic approach, inference of a signal depends first on an ‘a priori’ assumed signal mean and its variation. Following Bayes, this ‘prior distribution’ is combined with a likelihood distribution to produce a ‘posterior’ distribution describing the mean and the precision of the inferred signal. We propose that inference of circadian time-of-day can be described by a Bayesian framework, in which time-of-day depends primarily on the presumed prior time as determined by the internal pacemaker. This prior can be depicted as a Gaussian distribution with a width determined by the precision (in fact reliability) of the prior time-of-day estimate (top panel). Note that the horizontal time axis depends on the circadian period (which may be different from 24 h). Note also that these graphs do not represent the activity of the pacemaker; they merely specify the probability (y-axis) of a particular estimation of time-of-day (x-axis). The internal prior time-of-day distribution is combined with a likelihood distribution and a timing specified by external environmental entrainment time-of-day cues. Usually the internal pacemaker prior and the environmental entrainment signals are roughly in agreement (here they are misaligned for illustration).

whereas the dorsal SCN has a robust autonomous activity with a weak immediate light responsiveness. SCN targets receive information from both the ventral and dorsal regions of the SCN and it is important that the dorsal and ventral activity is synchronized to prevent dysregulation at targets downstream of the SCN.

Time-of-day cue-conflict: produced when multiple cues specify conflicting information about the time-of-day. Time-of-day cue-conflict is reflected by a desynchronization between the ventral (environmental) and dorsal (internal) pacemaking signals of the pacemaker, leading to health issues that we designated circadian-time sickness.

successfully used to generate theories for sensory processing and decision making (e.g., [13]; see [Box 1](#) for a straightforward conventional probabilistic analysis of time-of-day cue-combination for circadian pacing). Note that our probabilistic analysis ([Box 1](#)) is purely functional with no need to start off from a mechanistic implementation, as opposed to existing analyses (e.g., [14,15]).

To build an autonomously working pacemaker that is influenced by an environmental light–dark cycle, an engineer needs at least two units ([Box 1](#)): (i) a unit that generates a repetitive endogenous activity pattern that varies in magnitude during a circadian cycle, thereby providing a prior distribution for the time-of-day; and (ii) a light-responsive sensor unit that is connected to the environment, potentially via, for example, measurements of intensity, wavelength, or even temperature related to the environmental light across the circadian cycle. By quantifying the rate of change in light characteristics (illuminance or color) across the circadian cycle (e.g., at dawn) this unit can, in fact, assign a likelihood to time estimations depending on the rate of variation in light characteristics (a larger gradient meaning more reliability).

The Approach by the Brain

Turning to physiology, the central master pacemaker of the brain, constituted by the **hypothalamic suprachiasmatic nucleus** (SCN), comprises thousands of individual autonomous cellular oscillators containing genes that cyclically regulate their own expression. Although each of these cellular oscillators has an individual phase, they are coupled, together generating a

composite waveform — (the ensemble SCN output activity) that follows a predictable sinusoid-like wave pattern defining one circadian period [16,17]. An example of a signal that exhibits a reliable circadian rhythm is the core body-temperature that cycles between 36.5°C and 37.1°C in a highly predictable manner [18].

It is central to our cue-combination reasoning that the SCN comprises two separate compartments with distinct functionality: a ventral (core) and a dorsal (shell) compartment, each containing an ensemble of thousands of individual cellular pacemakers with a probabilistic activity distribution (Figure 1, Key Figure). The ventral SCN exhibits a strong immediate light responsiveness with a weak autonomous activity, whereas the dorsal SCN exhibits a weak immediate light responsiveness with a robust autonomous activity [19–21]. This combines the best of two worlds: the robust autonomous dorsal pacing activity mainly reflects stored prior circadian rhythmicity; the ventral pacing activity mainly constitutes an acute reflection of the solar photoperiod [22–24] and also its seasonal pattern [25–27].

Does the Brain Implement Probabilistic Principles?

We propose that the biological clock of the brain naturally implements a probabilistic combination of time-of-day cues. To be more precise, we argue that the composite ensemble activity of the thousands of individual pacemaker neurons within the ventral compartment of the SCN immediately reflects the changing light level of the environment, thereby providing a likelihood-distribution for the time-of-day. We similarly argue that the composite ensemble activity of the thousands of individual pacemaker neurons within the dorsal compartment of the SCN without immediate strong light responsiveness, reflects a robust repetitive endogenous pattern of prior activity. This activity varies in magnitude during the day, thereby providing a prior distribution for the time-of-day.

If a current circadian rhythm corresponds to the local environmental (solar) rhythm, the natural way to deal with a correct prediction in a probabilistic framework is to increase the assumed precision of the prior distribution one circadian cycle later by making the prior distribution more peaked [28,29]. In fact, this characteristic could physiologically arise naturally from the interactions within the ensemble of the coupled oscillators: due to the spreading of individual circadian cycles, some oscillators start their activity earlier, and others later, generating a wider SCN ensemble signal in summer than in winter [15], embodying a mechanistic implementation of the above statistical ensemble approach.

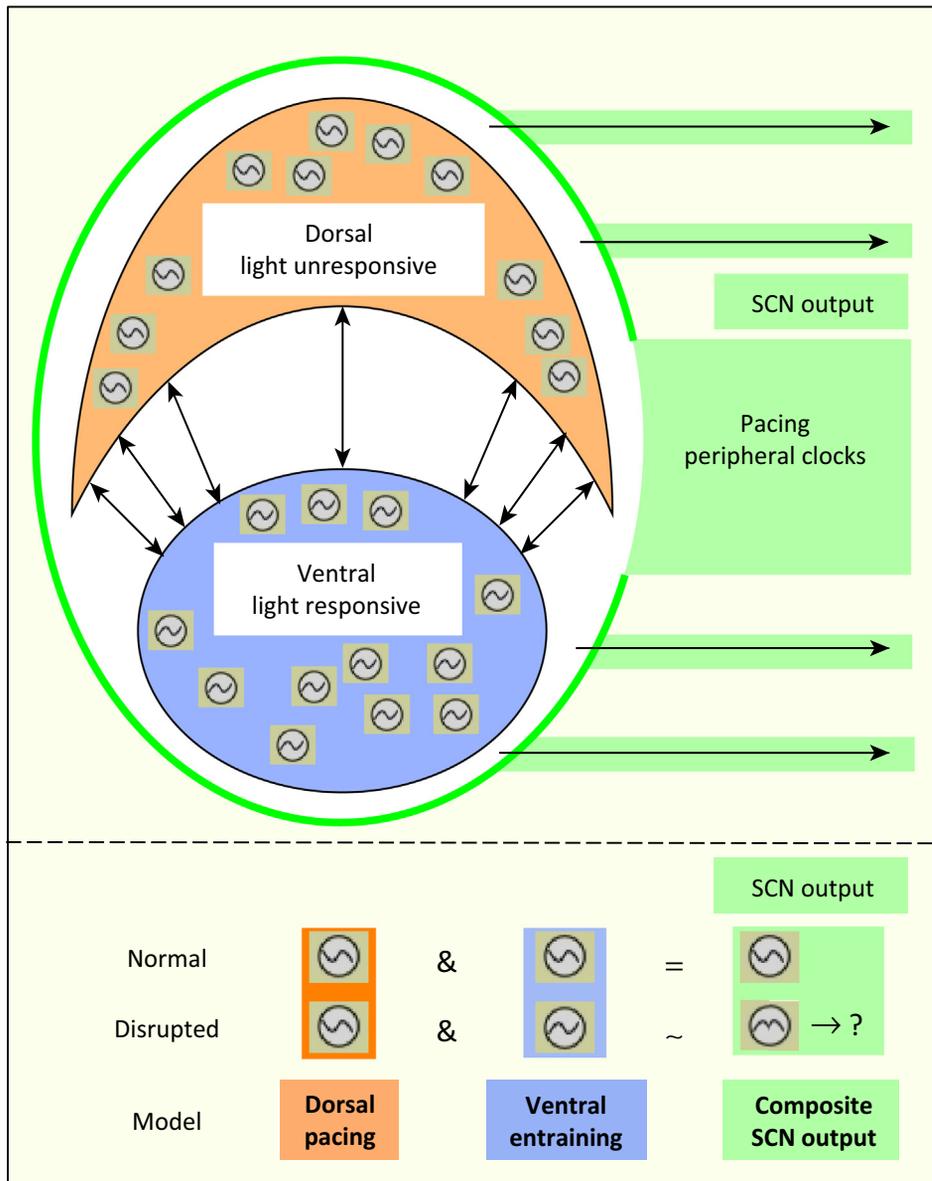
Nonphotic Entrainment of the SCN

So far, we have focused on the light–dark cycle (i.e., a photic signal) as the sole signal that entrains the SCN. Indeed, light is by far the most powerful entraining signal [30]. Theoretically speaking, also peripheral pacemakers may entrain the master pacemaker in the SCN. Restricted feeding, for example, phase-shifts the circadian rhythms of gene expression in the liver and kidney, uncoupling them from control by the SCN. However, while restricted feeding by itself can phase-shift peripheral pacemakers, eventually the peripheral pacemakers are reset by the central pacemaker [3]. Although synchronization between the central and peripheral pacemakers is important for optimal digestion for example, for a long time there appeared to be no convincing evidence for direct feedback connections from peripheral pacemakers into the SCN [3].

Nonphotic circadian signals now comprise a growing area of research [30]. Nonphotic physiological feedback signals into the SCN, influencing SCN activity, are reportedly related to neurotransmitter levels associated with neuropeptide and serotonin pathways [31], melatonin level [32], appetite-related ghrelin level [33], blood pressure [34], and behavioral activity [35]. In our Bayesian approach for time-of-day inference, there is essentially no difference whether one signal or multiple signals contribute to the entrainment of the SCN. In our equations (Box 1), we used a single time parameter for the internal signals (t_{int}) and one for the external signals (t_{ext}).

Key Figure

The Biological Clock of the Brain



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Figure 1. The suprachiasmatic nucleus (SCN), located in the hypothalamus, comprises a ventral (core) and a dorsal (shell) compartment. Each compartment contains thousands of coupled cellular oscillators and has a distinct functionality: the cellular oscillators in the ventral compartment are strongly light responsive, whereas the oscillators in the dorsal compartment have a weak, or no, immediate light responsiveness. When functioning normally, all the oscillators together generate a composite waveform that follows a predictable and reliable sinusoidal-like pattern during a circadian period. This sets the pace for the stress, alertness, and immune systems, as well as for peripheral pacemakers in organs throughout the body to optimally anticipate demands for energy. An abrupt shift in the light–dark cycle causes a temporary decoupling of cellular oscillators between the ventral and dorsal regions of the SCN. In this illustration, the two compartments contain oscillators in antiphase, leading to a bimodal (two-peaks) distribution.

This allows the presence of multiple internal and external signals, together comprising single distributions associated with internal and external time-of-day cues, respectively (Box 1).

Although there appears to be growing evidence that nonphotic cues contribute to entrainment of the SCN [30], one should keep in mind that their contribution need not be direct. Nonphotic signals may merely act as facilitators of the interaction between the ventral and dorsal SCN compartments. For example, the neurotransmitter vasopressin has a key role in this facilitation: in mice without vasopressin receptors, circadian rhythms of behavioral activity, pacemaker gene expression, and body temperature re-entrain immediately to light–dark-cycle modifications [36]. Stress induces release of vasopressin, making the dorsal part less sensitive to synchronization with the ventral part [37]. Physical exercise, or locomotion in general, influences vasopressin reciprocally, meaning that the dorsal part becomes more sensitive to the ventral part [38].

In the case of mere facilitation, the influence of nonphotic cues is limited to a gain factor (in theoretical terms, a gain factor gives increasing weight to a cue in cue-combination) that, in fact, regulates the strength of photic entrainment. This discussion invites future experimental studies that precisely control for the interaction of photic and nonphotic time-of-day cues on SCN entrainment.

Unnatural Light–Dark Shifts: Jetlag, Shift Work

Future experimental work could explore to what extent the probabilistic computations assumed by our normative probabilistic framework are implemented by the brain (see Outstanding Questions). We now turn the focus to unnatural light–dark shifts.

For our purposes here, it is key to emphasize that the cue-combination approach has important chronobiological implications for situations for which the brain has not been evolved: a sudden light–dark cycle shift, such as happens with jetlag or shift work (Box 2).

Both the ventral and the dorsal compartments project to targets downstream of the SCN [39,40]. This regulates the synchronization of peripheral pacemakers (liver, cortex, etc.) throughout the body [1–4] with the time-of-day-related biochemical and electrophysiological activity in the SCN [41,42]. In fact, most (if not all) SCN targets receive information from both the ventral and dorsal regions of the SCN [39]. Synchronized ventral and dorsal circadian pacing output provides a unique time-of-day stamp for the peripheral targets downstream of the SCN [40].

The immediate desynchronization between the light-related pacing (ventral SCN; likelihood) and the endogenous pacing (dorsal SCN; prior) after an abrupt large light–dark cycle shift can be sufficient as a physiological manifestation for a **time-of-day cue-conflict** within the pacemaker itself (Box 2 and Figure 1). The desynchronization produces a bimodal composite waveform [posterior P(T)C, Box 1], a bimodal ensemble SCN output activity, that is similar to the reported bimodality in visual perception under conflicting cues [43].

Indeed, several experimental studies demonstrated that the SCN composite output changed from a single-peaked distribution to a two-peak distribution upon an abrupt large light–dark cycle shift [44–46] (Figure 2). Within a few days, the SCN output returned to a single-peaked distribution that was synchronized with the new light–dark cycle [44–46] (Figure 2). A recent study corroborated these data by quantitative analyses at the level of neuronal subpopulation activity [47]. Ventral pacemakers fully readjusted to the shifted photoperiod already within a day, whereas the reset of the oscillators in the dorsal part [44–46] took several days (Figure 2).

For peripheral targets downstream of the SCN, a circadian pacing output of the SCN that is bimodally peaked constitutes a pacing unpredictability, possibly entailing hormonal and

Box 2. The Engineer's Adapting Circadian Clock

Consider an abrupt shift in the light–dark cycle, such as happens after a trans-meridian flight or with shift work; a situation for which the brain has not been evolved. Such a situation leads to the misalignment of prior and likelihood probability distributions (cue–conflict) and, thus, loss of predictability for pacemaking (Figure 1). The prior time-of-day distribution must be updated in such a case. Abrupt light–dark shifts force the brain into a situation that it has no generic controls for. The degree of behavioral control that an organism has over a stressor modulates the impact of the stressor [68,69].

Returning to the engineer, it is theoretically straightforward to build a pacing system that is adaptive under abrupt light–dark cycle shifts. New learning is necessary when the mismatch of 'likelihood' (environmental) and 'prior' (internal) time-of-day is beyond a threshold defined by reasonable noise levels. In this case, the precision of the prior should be decreased so that the impact of environmental cues (new evidence) increases, thus enabling faster updating [70,71]. This implies the use of a hierarchical Bayesian model that includes estimation of hyperparameters [70,71] or Kalman filters (e.g., [29]) with dynamic gain.

However, fast and flexible updating (by using a hierarchical model) would require extra neural resources. Given that the brain evolved in an environment without abrupt solar light–dark shifts, the pay-off of supporting increased flexibility most likely did not outweigh the risk of reduced robustness introduced by a hierarchical system. In fact, there are molecular inhibition mechanisms that slow down the effects of a phase-shifted light–dark period [36], so that full adjustment to a considerable phase-shift in the light–dark cycle requires multiple light–dark periods.

The biological solution with direct interactions between the many ventral and dorsal oscillators that the SCN appears to have followed in principle obviates the need for a neuronal unit that monitors whether the environmental light–dark cycle is shifted relative to the endogenous circadian cycle. Note, however, that a direct interaction of the ventral and dorsal compartments within the SCN does not exclude the possibility of also having a separate, third, monitoring neuronal center reflecting the desynchronization between the light-responsive and the light-unresponsive compartments. Interestingly, recent work shows emotion-related amygdala activity in response to light pulses at night [6]. It may be possible that the amygdala acts as a unit that responds to (or even monitors) such conflicting information.

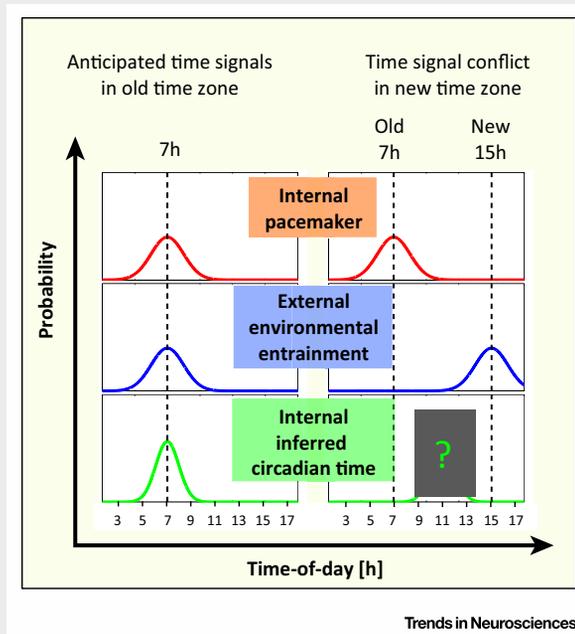
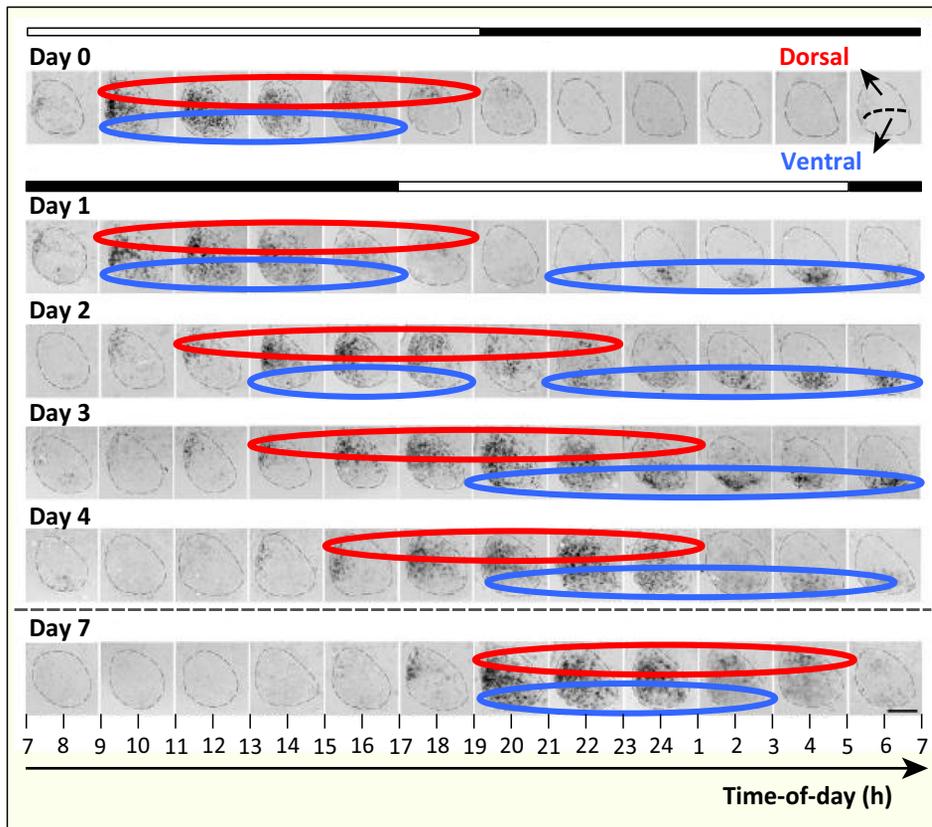


Figure 1. Jetlag Entails Cue-Conflict. During jetlag (here 8 h, for west-to-east travel; 2nd column), there is a conflict between the time-of-day (within circadian period) specified by the pacemaker (prior, top panel) and the local time in the new destination time zone (likelihood, middle panel). Indeterminate time inference results when the distributions of the internal and the environmental specified time do not match. The prior time-of-day distribution must be updated in such a case.



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Figure 2. Bimodal Pacemaker Activity. Clock gene expression (*Per1*, a marker of internal clock phase) in coronal brain slices of rat suprachiasmatic nucleus (SCN) after an abrupt phase delay (10 h) in the light–dark cycle. The top black-and-white bar specifies the original light–dark cycle, whereas the bottom bar shows the shifted cycle. The broken line specifies the SCN. The top side of the SCN is the dorsal part (red), whereas the bottom side is the ventral part (blue). The environmental time is specified below the columns. On the day before the light–dark cycle shift, the clock gene expression of the ventral (illustrated roughly by blue ellipse) and dorsal (red ellipse) compartments was synchronized. On the day after the shift, the two compartments became initially desynchronized (bimodal) and became gradually resynchronized. Scale bar = 200 μ m. Reproduced from [45].

neuronal signals that are inappropriately timed, occur multiple times a day, or do not occur altogether (Box 2). In other words, desynchronization between the ventral and dorsal pacing activity ought to induce dysregulation for peripheral targets downstream of the SCN, including those targets that regulate behavior. Indeed, it has been reported that exposing rats to a 22-h light–dark cycle (using a forced desynchrony protocol) induced two circadian behavioral motor activity rhythms [40]. Analysis of SCN gene expression for this so-called ‘splitting’ in motor activity suggested, in support of our reasoning, that the two motor activity rhythms reflected the separate activities of the desynchronized ventral and dorsal SCN compartments [40].

Unnatural Light–Dark Cycles Directly Affect Health

Recent work by Hattar and colleagues was the first to convincingly demonstrate that an unnatural light–dark cycle in-and-of-itself can result in health issues [7]: mice subjected to an aberrant light–dark cycle showed a significant increase in behavioral stress and depression-like behavior [6]. Crucially, the circadian periods in core body temperature and behavioral activity (\sim 24 h), as well as the amount of sleep, remained roughly unaffected by the aberrant light–dark cycle [6,7]. Thus, the aberrant light–dark cycle must have exerted its influence on well-being irrespective of the sleep duration and the circadian period [6,7]. Interestingly, their data also

demonstrate an increased variability in core body temperature and locomotion during a circadian cycle, which is consistent with a deteriorated synchrony between the ventral and dorsal compartments of the SCN under the aberrant light–dark cycle, as predicted by our approach.

Another recent study exposed mice to a 20-h light–dark cycle [48], demonstrating a loss of rhythmicity in several measures, including sleep (but not in total sleep period), as well as modified levels of immune responses both in the brain and the periphery after a bacterial endotoxin challenge. These findings further emphasize that an unnatural light–dark cycle increases vulnerability to environmental stressors [48], thereby compromising optimal conditions for health.

Circadian-Time Sickness

The biological clockwork of the brain has evolved without exposure to sudden light–dark shifts and has never faced a natural environmental cause for a desynchronization of the ventral and dorsal SCN activity. In other words, for the brain, such desynchronization ought to be indicative of malfunctioning internal clockwork, seriously endangering metabolic and behavioral timing that is critical for survival.

Returning to motion sickness: initially, the scientific literature did not provide a neural mechanistic principle that would have predicted that conflicting vestibular and motion signals would lead to low mood and nausea. Similarly, no known mechanistic principle would have predicted the stress and depression-like behavior [6] and the deteriorated immune responses [48] under an unnatural light–dark cycle. The normative Bayesian approach does provide such a principle: a sustained conflict between ‘prior’ and ‘likelihood’ probability distributions leads to unpredictability, bringing the brain to a state that lacks a scenario for keeping control.

For putting on new spectacles, with accompanying 3D distortions, remapping of prior stereoscopic information has been identified as the key element to overcome the perceptual cue-conflict caused by the new spectacles [11]. Circadian pacing constitutes a novel perspective on a cue-conflict situation where a similar remapping of prior information (shift of dorsal activity) appears to be in place. We argue that the unpredictability caused by time-of-day cue-conflict in-and-of-itself can lead to health issues that we designate as ‘**circadian-time sickness**’.

One may reason that a range of findings in the literature on sickness under disrupted light–dark cycles could potentially be understood as circadian-time sickness. For example, disrupted circadian rhythmicity has been associated with obesity, diabetes, cardiovascular diseases [3,4], accelerated neurodegeneration with aging [49], Alzheimer disease [50,51], psychiatric mood disorders [51–54], as well as with the progression of cancer [55] and the success of anticancer treatments [56]. Although some of these studies have argued that the sickness is unrelated to the length of the total sleep period [49], these studies do not yet convincingly support our cue-conflict approach because a direct role of an unnatural light–dark cycle was not dissociated from the circadian and sleep periods (such as Hattar and colleagues [6] recently did), warranting future studies (see Outstanding Questions).

A recent study, in which mice were exposed to long-term continuous light, recorded SCN neuronal activity in combination with the monitoring of health parameters [57]. The continuous light exposure had detrimental effects on a range of health parameters (reduced skeletal muscle function, bone deterioration, and proinflammatory state). The neuronal recordings revealed that the pacemaker neurons in the SCN exhibited flattened circadian activity. After returning to a standard light–dark cycle, the pacemaker neurons rapidly recovered their normal high-amplitude rhythm, and the health parameters reverted to normal [57]. Also in this study, the detrimental effects in health-related parameters cannot be dissociated from potential changes in the sleep

period. However, the important message is that a long-term unnatural light exposure can cause flattened circadian variation in activity of pacemaker neurons in SCN, thereby triggering serious health issues.

Application

Practical recipes on how to optimally adjust a phase shift of the central master pacemaker due to jetlag or shift work comprise a considerable literature [51,58]. Here, we put such recipes in a normative perspective by taking the prior SCN activity into account. Personal optimization of a recipe is possible and requires determination of the individual's circadian clock rhythm (e.g., through measurements of core body temperature [18]) to minimize the extent of desynchronization between the ventral and dorsal outputs of the SCN and to apply environmental time-of-day cues at time points where they are most influential. Bayesian inference imposes the key insight to consider both the prior (reflecting endogenous circadian cycle) and the likelihood activity (reflecting environmental circadian light-dark cycle) when developing strategies to minimize time-of-day-related cue-conflicts. Given that the relative precisions (inverse variances) of prior and likelihood determine the degree to which new incoming (photic) evidence updates prior estimates, interventions that influence these precisions can be expected to affect the speed of adaptation to a new light-dark regime.

Such insights have clinical relevance. For example, circadian timing regulates cell proliferation and can be of paramount importance in cancer development and therapy [59,60]. Another clinical example involves neonatal intensive-care units: infants maintained in a well-defined 24-h light-dark cycle, thus minimizing time-of-day cue-conflict, gain weight significantly faster, resulting in an almost 50% shorter hospital stay than infants in conventional incubators applying constant light [61,62]. For older humans, fragmentation in intraday and interday circadian behavioral activity rhythms, but not total sleep duration, reportedly predicts mortality [8,63]. Integration of marked light exposure rhythmicity in the daily routine of older humans, minimizing time-of-day cue-conflict, has been shown to ameliorate several measures associated with depression and cognitive decline ([64–66]; E.I.S. Most, PhD Thesis, Vrije Universiteit, 2013. For review of older work see [9]; also see Outstanding Questions).

Concluding Remarks

Understanding how the genesis and persistence of disturbances in mood, well-being, and health may depend on the master pacemaker of the brain can have a vital impact for many individuals. The SCN, with its large ensembles of cellular pacemakers, by itself can naturally implement normative probabilistic weighting of internal prior (dorsal) circadian pacing activity against the likelihoods of external (ventral) updating time-of-day cues. While it is generally recognized that synchronization between the various peripheral clocks throughout the body (e.g., for digestion, cell division, and sleep) is key for optimized functioning [9], we add to this literature an even more fundamental aspect: namely the need for synchronization between the two internal (ventral and dorsal) SCN pacing activities. We reasoned that a lack of such synchronization, involving unpredictability following a time-of-day cue-conflict, disturbs reliable time-of-day-dependent pacing for targets downstream of the SCN, entailing circadian-time sickness.

The Bayesian cue-conflict approach presented in this Opinion describes the circadian timing system without the need for a specific neuronal center that monitors and corrects the phase of the clock when it is not in synchrony with the environmental light-dark cycle. A popular analogy in chronobiology compares the biological clock with an orchestra comprising many individual soloists, and various sections, such as a rhythm section, that influences other sections [67]. Interestingly, the biological solution suggested here, in which two SCN units are sufficient, statistically weighting the external light-related SCN activity against the internal, stored SCN activity, obviates the need for a homuncular conductor of the orchestra.

Outstanding Questions

To what extent is a probabilistic framework for circadian pacing implemented by the brain? For example, does the weight given to a likelihood cue depend on its variability? Such a question invites an experiment in which the circadian and sleep periods are controlled for, and where the reliability of light-related time-of-day cues are perturbed.

Do individual differences in health issues after jetlag, or shift work, correlate with individual differences in core body temperature variation? According to probabilistic reasoning, more variation implies less time-of-day cue-conflict under an aberrant light-dark regime.

Does a history of time-of-day cue-conflicts influence the sensitivity to subsequent exposure to such cue-conflict?

To what extent do feedback signals from peripheral physiological processes contribute to time-of-day inference of the SCN?

The prevalence of cardiovascular disease, obesity, and diabetes correlates with disrupted circadian pacing and unnatural light-dark cycles. Does this correlation still hold when the circadian and sleep periods are controlled for?

Early literature noted that psychiatric disease associates with disrupted circadian rhythm of core body temperature. Is there a link between increased risk of mental illness and circadian rhythm disruption?

Can neurodegeneration of the SCN with aging contribute to a desynchronization between the ventral and dorsal pacing that, in turn, contributes to health and mood problems with aging?

To what extent do optimal theory-driven light-dark regimes (i.e., that take into account a person's prior SCN cycle) expedite the overcoming of circadian-time sickness?

Recent work shows amygdala activity in response to light pulses at night. Is an alternative theory possible where the amygdala acts as a conflict monitoring unit, detecting when light registered by the retina conflicts with the estimate of the SCN of nighttime? This

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Supplementary data

Supplemental information associated with this article can be found online at doi:10.1016/j.tins.2016.09.004.

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question invites experiments that dissociate the SCN activity from retinal activity.

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