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CHAPTER 9

Dynamic neuronal network organization of the circadian clock and possible deterioration in disease

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Abstract: In mammals, the suprachiasmatic nuclei (SCNs) function as a circadian pacemaker that drives 24-h rhythms in physiology and behavior. The SCN is a multicellular clock in which the constituent oscillators show dynamics in their functional organization and phase coherence. Evidence has emerged that plasticity in phase synchrony among SCN neurons determines (i) the amplitude of the rhythm, (ii) the response to continuous light, (iii) the capacity to respond to seasonal changes, and (iv) the phase-resetting capacity. A decrease in circadian amplitude and phase-resetting capacity is characteristic during aging and can be a result of disease processes. Whether the decrease in amplitude is caused by a loss of synchronization or by a loss of single-cell rhythmicity remains to be determined and is important for the development of strategies to ameliorate circadian disorders.

Keywords: circadian; SCN; network; plasticity; synchronization; entrainment; photoperiod; jet lag; aging; circadian disorders.

Introduction

Most animals show clear 24-h rhythms in physiology and behavior. These rhythms have developed as an adaptation to the recurring changes in the environment, brought about by the rotation of the earth around its axis. In order to anticipate these changes, innate clocks have evolved that allow organisms to prepare for the predictable onset of night and day. In mammals, the central clock is located in the suprachiasmatic nucleus (SCN). The SCN is a bilateral structure, located at the base of the brain, with the ventral aspect immediately above the optic chiasm. The SCN contains about

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10,000 neurons on each side and maintains direct and indirect connections with many parts of the central nervous system (Kalsbeek et al., 2006; Morin and Allen, 2006). Light is the major external stimulus that synchronizes the endogenous clock to the external 24-h cycle. It reaches the neurons of the SCN via a monosynaptic pathway, formed by melanopsin containing retinal ganglion cells (Berson et al., 2002; Hattar et al., 2003), that project with glutamate- and PACAP-containing fibers to the SCN (Golombek and Rosenstein, 2010; Hannibal et al., 2000). A distinction has been made in the core and shell region of the SCN (Antle and Silver, 2005; Gamble et al., 2007; Ibata et al., 1989; Kiss et al., 2008; Moore and Silver, 1998). The core contains gastrin-releasing peptide (GRP)- and vasoactive intestinal polypeptide (VIP)-expressing neurons and is retinorecipient (Abrahamson and Moore, 2001; Antle et al., 2005). The shell contains vasopressin and receives input from the core of the SCN (Moore et al., 2002), while the core is only sparsely innervated by the shell (Romijn et al., 1997).

Generation of circadian rhythmicity occurs at the single-cell level and is based on an intertwined negative feedback loop between clock genes and their protein products (Herzog, 2007; Reppert and Weaver, 2002). The genetic basis for rhythm generation can explain that isolated cells of the SCN are capable of generating circadian rhythms and do not require rhythmic input (Webb et al., 2009; Welsh et al., 1995, 2010). The important implication is that the SCN functions as a multi-oscillator structure in which the different neurons are mutually synchronized in phase in order to function as a coherent pacemaker. In this chapter, we review the role of synchronization within the SCN for the functional adaptation of the SCN as a clock and cover specific questions: How is the multioscillator structure used for the adaptation to shifts of the light–dark cycle? What is the response of the SCN to constant light and to seasonal changes? What are the consequences of changes in neuronal synchrony for rhythm waveform, amplitude, and resetting capacity? Finally, we raise the possibility that one mechanism by which aging and disease can alter the function of the circadian system is by reducing the strength of the intracellular coupling within the SCN circuit.

SCN waveform is an ensemble property

Recordings of electrical impulse frequency have been performed both *in vivo* in the intact animal and *in vitro* in brain slices that contain the SCN. Pioneers of SCN *in vivo* recordings were Inouye and Kawamura (1979) who performed these recordings to show that the SCN functions as an endogenous oscillator. SCN *in vitro* recordings confirmed that the SCN functions as an endogenous oscillator and does not require rhythmic input to sustain rhythmicity (Green and Gillette, 1982; Groos and Hendriks, 1982; Shibata et al., 1982). A consistent finding of *in vitro* and *in vivo* electrophysiological recordings is that during the day, electrical activity is high, and during the night it is low, both in nocturnal and in diurnal species. In nocturnal animals, high activity of the SCN corresponds with the resting phase and low activity with the active phase of the animal (Brown and Piggins, 2007; Colwell, 2011; Gillette, 1996). In diurnal species, this is reversed and electrical activity is in phase with the behavioral activity pattern (Challet, 2007). A major difference between nocturnal and diurnal animals is therefore the phase relationship between the SCN and other parts of the central nervous system.

The waveform of the SCN electrical activity rhythm is almost sinusoidal. Simultaneous recordings of electrical activity and behavioral activity have allowed us to determine at what level of electrical activity, behavior is initiated or arrested (Houben et al., 2009). The onset of activity appears to occur at around the 50% level of the rhythm amplitude. Within a certain range around the 50% level, the chance for a transition from rest to activity is maximal. Also for the offset of activity, a close correlation with the 50% level is observed. It is concluded that the

on- and offset regulation of behavioral activity is rather predictable from the level of SCN electrical activity and suggests a direct relationship between SCN neural activity and the onset–offset of behavioral patterns. These findings have implications for situations in which the waveform of the SCN changes, which will be discussed in this chapter.

The waveform of the SCN molecular and electrical activity reflects the combined activity of many neurons and is thus a composite tissue-level property (Evans et al., 2011; Maywood et al., 2006; Quintero et al., 2003; Schaap et al., 2003; Yamaguchi et al., 2003; Yamazaki et al., 2000). Decomposition of the ensemble pattern has revealed that small subpopulations and single SCN neurons exhibit much shorter periods of enhanced electrical activity. Single units in the mouse and rat SCN appear to be active for durations of about 5 h (Brown and Piggins, 2009; Brown et al., 2006; Schaap et al., 2003; VanderLeest et al., 2007). The time of maximal activity of most neurons of the SCN is during the day, but some neurons are active during the night (Fig. 1). The distribution of individual neuronal activity patterns can account for the ensemble pattern of the SCN, as the highest density of active neurons occurs during midday, while the lowest density of active neurons occurs at midnight. This phase distribution renders a sinusoidal pattern in SCN multiunit activity at the ensemble level.

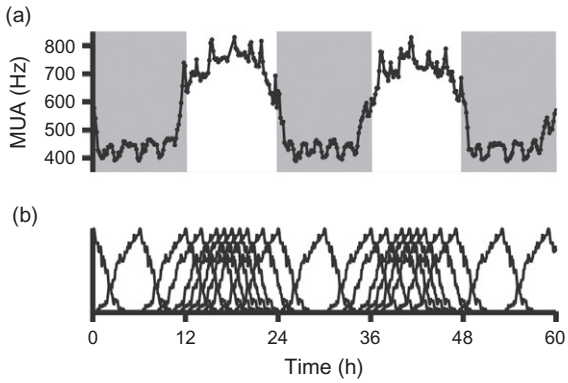

Fig. 1. Distribution of single neuron electrical activity pattern explains the multiunit electrical activity pattern of the SCN. (a) An *in vivo* electrical activity recording of 60 h, with the gray background indicating night and the white background indicating day. (b) One typical recording of an electrical activity pattern of a mouse housed in a 12:12 light–dark cycle was used and plotted repetitively according to a Gaussian distribution, to simulate the phase distribution of neuronal activity patterns in the SCN. The electrical activity pattern of the population renders the characteristic multiunit electrical activity pattern.

Constant light effects

Exposing organisms to continuous light causes robust changes in the circadian rhythms including a strong reduction in the amplitude of overt rhythms, lengthening of the endogenous cycle length (period) (Aschoff, 1979), and can even lead to splitting of circadian locomotor behavior and arrhythmicity (Depres-Brummer et al., 1995; Eastman and Rechtschaffen, 1983; Pittendrigh and Daan, 1976). Previous data suggest that the impact of constant light is to desynchronize single-cell oscillations. For example, recordings from individual SCN cells *in vitro* of rhythms in *Period1* promoter-driven GFP fluorescence rhythms have revealed that individual neurons from arrhythmic mice kept in constant light are not compromised in their rhythm-generating ability (Ohta et al., 2005). In fact, the individual neurons remained rhythmic, but the population shows a severely distorted phase distribution. The strong disruption of phase coherence by exposure to constant light leads to a decline in circadian amplitude at the tissue level. Similarly, *in vivo* recordings in the SCN of mice kept in continuous light result in reduced overt rhythmicity and confirm these findings for electrical activity of the SCN. These recordings revealed a gradual decline in amplitude and a distortion of electrical rhythmicity upon prolonged exposure to continuous light (Fig. 2). The results show the necessity of coupling mechanisms, in addition to the presence of rhythm-generating units, and indicate the vital importance of the network-level

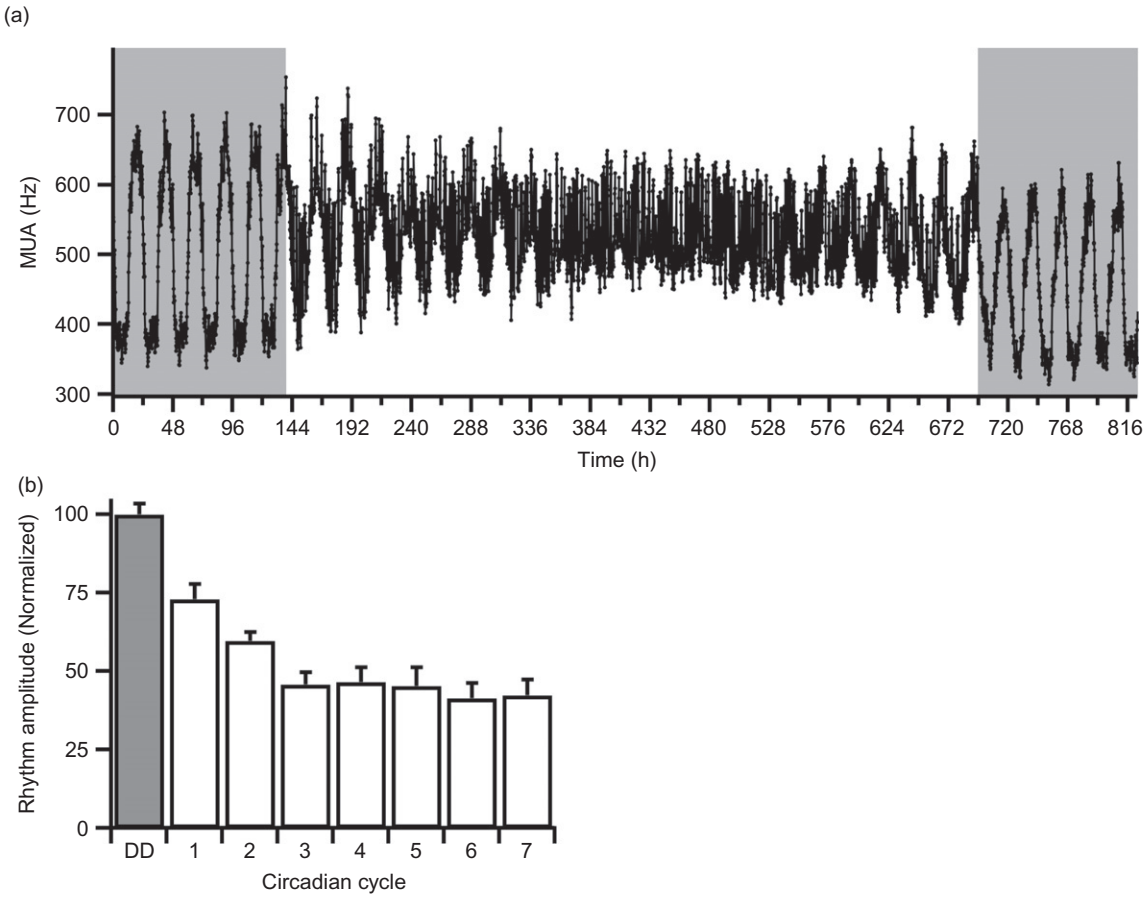

Fig. 2. Effect of constant light on SCN neuronal activity and behavior. (a) Long-term *in vivo* recording of SCN neuronal activity in a freely moving mouse. SCN activity was recorded with implanted microelectrodes and is depicted in 10-min bins (black trace). Gray background indicates lights off and white background lights on. During the first days in constant light, a decrease in amplitude is observed. During prolonged exposure to constant light, the amplitude of the rhythm was variable as the SCN appeared to lose and then regain coherence. This may reflect temporal synchronization and desynchronization of the constituent oscillators. (b) Effect of constant light on the mean amplitude of the SCN rhythm in seven animals. The animals were exposed to LL for at least 7 days following exposure to constant darkness. The rhythm was normalized for each animal and expressed relative to the amplitude in constant darkness (gray bar, ±SEM). White bars depict the amplitude during the first 7 days in constant light.

organization of the SCN to obtain robust and high-amplitude rhythms.

Synchronization among the neurons of the SCN is critically determined by a variety of coupling mechanisms (for review, see Welsh et al., 2010). Several coupling factors have been implicated such as VIP, GABA, and even gap junctions. These factors determine the phase coherence within the SCN and hence influence the waveform of the ensemble rhythm. Coupled oscillator models have found that large groups of oscillators such as SCN neurons can organize themselves into many different configurations to meet environmental challenges. These conformational changes are

rapidly driven by alterations in the strength of neuronal coupling mechanisms (Golubitsky et al., 1999; Strogatz, 2003; Strogatz and Stewart, 1993). The flexibility in coupling strength between neuronal populations enables the system to cope with different environmental conditions such as changes in the light–dark cycle and responses to constant light. In the next section, we will consider how changes in day length affect the phase synchrony among SCN neurons.

Seasonal changes in waveform by changes in phase distribution

In response to the changes in day length that occur over the course of the year, many animals undergo strong alterations in their anatomy, physiology, and behavior. Seasonal breeding organisms show drastic changes in behavioral activity, metabolism, and reproductive physiology (Ebling and Barrett, 2008; Hazlerigg and Loudon, 2008). The duration of the melatonin signal is a critical cue for some seasonal breeders, while other seasonal adaptations do not appear to be driven by melatonin. To provide an example, C57 mice have very low melatonin and yet display robust photoperiodic driven changes in behavioral activity. When these mice are exposed to long or short photoperiods, the duration of activity (alpha) is systematically lengthened in short days and shortened in long days. The changes in alpha are maintained even when the mice are placed in constant darkness. The behavioral activity pattern that is then displayed reflects the previous photoperiod, indicating an endogenous memory, or encoding mechanism, which is present for days to weeks (Sumova et al., 2004).

The SCN plays an important role in the seasonal encoding process. The sinusoidal-like waveform of the SCN electrical activity profile is strongly altered under influence of long and short days, as shown by *in vivo* recordings of the SCN, or by *in situ* analysis of clock gene expression. The electrical activity profile becomes compressed (narrow peak) in short days and decompressed (broad peak) in long days (Houben et al., 2009; Mrugala et al., 2000). The same modulation at the tissue—or population—level is observable in a number of clock genes (Carr et al., 2003; Johnston et al., 2003, 2005; Nuesslein-Hildesheim et al., 2000; Sumova et al., 2002, 2003; Tournier et al., 2003), Fos expression (Jac et al., 2000b; Sumova et al., 1995; Vuillez et al., 1996), and vasopressin (Jac et al., 2000a) and prokineticin 2 (PK2) mRNA levels (Cheng et al., 2005). The peak width appears to serve as an internal representation of the length of the day. Importantly, the photoperiodic driven changes in the SCN waveform and activity patterns are maintained for weeks even when the animal is released back into constant conditions. We view these changes as a type of plasticity in SCN physiology.

While photoperiodic encoding of day length is explainable by the change in the width of the electrical activity peak, a valid question is whether also changes in triggering level account for the modulation in activity duration. Presumably, a higher triggering level would result in an increase in the activity period and a lowering of the triggering level in an increase in the activity duration. This mechanism was proposed by Wever (1960) as a possible underlying mechanism for modulation of long- and short-activity periods in finches. In order to explore this possibility, we have recorded the SCN *in vivo* under long and short photoperiods and have simultaneously scored the onset and offset of behavioral activity (Houben et al., 2009). However, we found no evidence for changes in triggering level, and instead, we observed that both in long and in short days, transitions between activity to rest were most likely to occur at 50% of the electrical activity rhythm. We conclude that the change in peak width represents the major mechanism by which photoperiod is internally encoded by the SCN, and that no changes in triggering level are involved.

The plasticity in the waveform of the SCN, observable in behavioral activity patterns, and in the SCN *in vivo* is preserved when the SCN is

recorded *in vitro*, in a brain slice preparation (Mrugala et al., 2000). This finding opens up the important possibility to investigate the mechanism underlying SCN waveform changes *in vitro*. Two studies have independently proposed that SCN neurons show oscillations in their molecular or electrical activity pattern that are out of phase and that these phase differences could contribute to the photoperiodically induced changes in waveform (Quintero et al., 2003; Schaap et al., 2003). These predictions were confirmed in recordings of subpopulations of individual SCN neurons from mice held in different photoperiods (Brown and Piggins, 2009; Hazlerigg et al., 2005; Inagaki et al., 2007; Naito et al., 2008; Sosniyenko et al., 2009; VanderLeest et al., 2007). These studies all found evidence that exposing mice to long days causes a desynchrony in the electrical activity and gene expression rhythms within the SCN (Fig. 3).

Surprisingly, the neural activity patterns recorded from individual SCN neurons show little change in their activity pattern in long and short days (Brown and Piggins, 2009; Naito et al., 2008; VanderLeest et al., 2007). Photoperiod changes primarily the phase distribution but not the duration of electrical activity within individual cells. While Brown and Piggins (2009) observed longer duration activity of cells in the dorsal SCN under long days, they also showed that these changes render very little difference in the duration of the population activity pattern in agreement with simulations and predictions from other studies (Rohling et al., 2006a,b).There is consensus on the conclusion that the increment in the active duration of the population is caused by changes in phase distribution, rather than by changes in single-cell activity pattern.

As a consequence of this decreased synchrony in long photoperiods, neural activity rhythms are broader and exhibit a lower peak–trough amplitude. In contrast, exposure to short days leads to enhanced synchrony among SCN neuronal populations with a resulting narrowing of the peak and increased amplitude of the SCN rhythm.

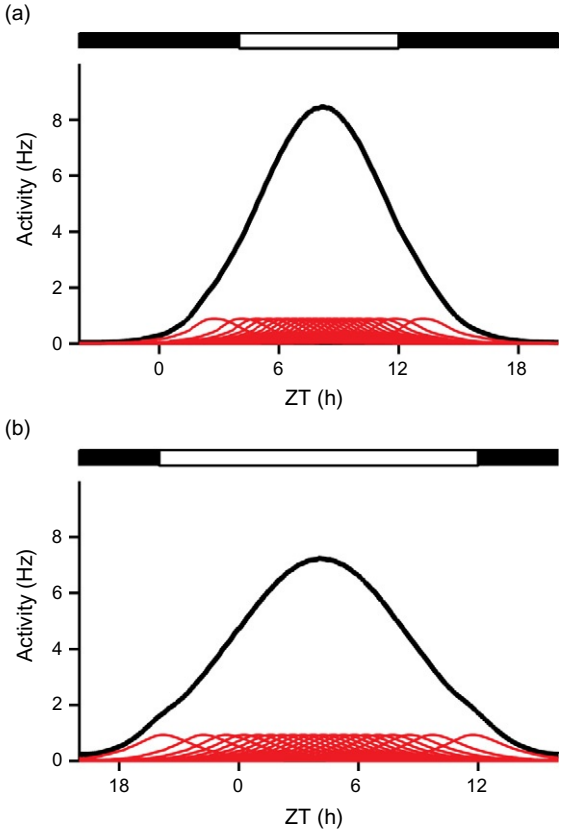

Fig. 3. The distribution of single-unit electrical activity patterns is responsible for the difference in multiunit electrical activity pattern in long and short photoperiod. The multiunit electrical activity pattern in short (a) and long (b) photoperiod is shown as a thick black line. This pattern is derived from an ensemble of single-unit activity patterns that are distributed over the 24-h cycle according to a Gaussian distribution. The single-unit activity patterns for short and long photoperiod were determined from a number of recorded single-unit activity patterns (25 for short photoperiod, 22 for long photoperiod). The half-maximum values of the single-unit patterns were determined and the time-point that expressed the middle between both half-max values was used to align all single-unit patterns. The mean of all aligned single-unit patterns was then determined, and these averaged single-unit patterns were distributed over the 24-h cycle according to a narrow Gaussian distribution for short photoperiod (a) or broad Gaussian distribution for long photoperiod (b). The multiunit activity pattern was determined by summating these distributed single-unit activity patterns. Above the figure, the light–dark schedule for each photoperiod is shown.

Phase-shifting capacity as a function of neuronal synchrony

The photoperiod to which animals have been exposed determines the phase-shifting capacity of the circadian system. The impact of photoperiod on the amplitude of the phase response curve (PRC) was first demonstrated by Pittendrigh and coworkers (1984). Hamsters kept on short days exhibited a larger amplitude PRC than animals kept on long photoperiod. The findings (also see Evans et al., 2004; Refinetti, 2002) raise questions about the underlying mechanisms. One possibility is that long light exposure desensitizes the retinal ganglion cells to light, and that the smaller shifts in long days reflect a difference in retinal light response. In a recent study, we exposed mice to short and long photoperiods but doubled the hourly number of photons in short photoperiods (VanderLeest et al., 2009). Accordingly, the animals received the same amount of photons in long and short photoperiod but distributed over a different time span. No decline in the phase-shifting response was observed in the short days, and the response remained significantly larger than in long days. Although other interpretations are possible, these findings provided a first indication that retinal information processing is not responsible for the photoperiod-driven changes in the magnitude of light-induced phase shifts.

The other possibility is that the difference in phase-shifting capacity is not determined at the level of the retina but is determined at the level of the SCN neuronal network. In this case, the difference in phase-shifting capacity observed in long and short days should be preserved *in vitro*. To test this, we prepared brain slices from mice held on long and short photoperiods and examined the phase-shifting effects of the application of NMDA. A variety of evidence suggests that NMDA receptors are critical for light-induced phase shifts and we, and others, have found that bath application of NMDA can produce phase shifts in the neural activity rhythms (Ding et al., 1994; VanderLeest et al., 2009). While the acute response to NMDA was not different in the short- and long-day preparation, the phase-shifting effect was significantly larger in slices from short days. The data indicate that reduction in the magnitude of phase shifts observed in long days is intrinsic to the SCN network organization.

In long days, the neuronal populations of the SCN are desynchronized, yielding an ensemble pattern with a low-amplitude rhythm. In short days, the neurons are highly synchronized in phase, leading to a high-amplitude rhythm of the population. Our finding that large shifts are obtained under conditions in which the neural activity rhythm is exhibiting a high-amplitude rhythms is in some ways surprising in that it does not fit predictions from the limit cycle oscillator theory that the magnitude of the phase shift is inversely related to the amplitude of the rhythm (Pittendrigh et al., 1991; Pulivarthy et al., 2007). This assumption is based on the notion that a perturbation of similar strength changes the phase angle of a low-amplitude rhythm more than the phase angle of a high-amplitude rhythm because the perturbation is a larger fraction of the radius of the cycle. This prediction has been confirmed in many biological (and nonbiological) systems and is valid for single-cell rhythms (*Gonyaulax*: Johnson and Kondo, 1992; *Neurospora*: Johnson, 1999; Lakin-Thomas et al., 1990). We believe that the results of vanderLeest et al. (2009) show that the limit cycle theory does not hold for the network of the SCN in explaining differences in phase-shifting capacity in long and short days.

Instead, we favor the view that under long-day conditions, the SCN network is desynchronized and the individual neurons receive the NMDA pulse at different phases of their circadian cycle, leading to diverse phase-shifting responses. When the neurons are more synchronized, they would respond more consistently, leading to a larger net-shift of the ensemble. Using computer simulations, we have found that the phase-shifting response of the population can be simulated by distributing neurons over the cycle, according to the observed phase distribution in long and short

days (VanderLeest et al., 2009). We supposed that the individual neurons showed limit cycle oscillator behavior, and that they had the same PRCs. Distribution of neurons, in the simulations, was therefore similar to distribution of PRCs. Because the PRCs of individual SCN neurons are not known, we gave the neurons either type 1 or type 0 PRCs, to test the feasibility of our explanation (but only one type per simulation). When we distributed neurons according to the distribution observed in long photoperiods, the delaying and advancing parts of the PRC do not fully overlap. As a result, a particular pulse will lead to delays in some neurons, but to advances in others. The net result of these divergent shifts is a minor shift of the population as a whole. When the PRCs are fully synchronized, a particular pulse will lead to a unidirectional shift in all neurons, and the net result will be a much larger phase response of the population (Fig. 4).

We are aware that the present simulations present only one possible explanation for the observed difference in phase response magnitude in long and short days which needs to be confirmed experimentally. Notwithstanding, it has become clear that in the neuronal network of SCN oscillators, at least one prediction of the limit cycle oscillator theory does not hold, that is, the larger amplitude rhythms showed the larger instead of the smaller phase-shifting responses. The experiments demonstrate that properties emerge at the population levels that are not present at the underlying single-cell level.

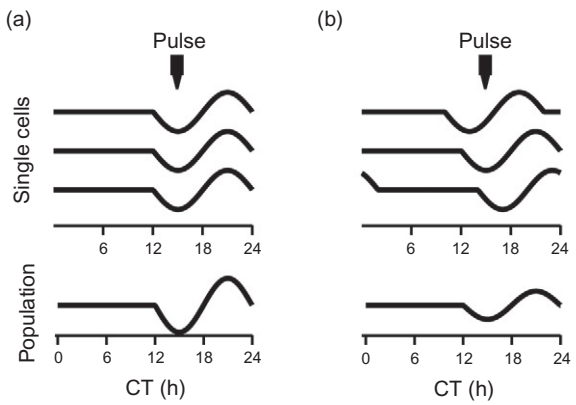

Fig. 4. Distributed single-cell phase response curves (PRCs) determine the ensemble PRC. If the single-cell PRCs are all in the same phase of the cycle, the resulting ensemble PRC will have a large amplitude as a single light pulse (arrow) will trigger a similar phase-shifting response in all cells (a). If the single-cell PRCs are out of phase, the resulting ensemble PRC will have a lower amplitude as the cells will have divergent responses (b).

Phase resetting is driven by a small population of highly synchronized neurons

Shift work and jet lag cause a temporal disruption of circadian rhythms that are evidenced by sleep disturbances, intestinal problems, and fatigue (Arble et al., 2010; Eastman and Burgess, 2009; Waterhouse et al., 2007). Animals have been exposed to an abrupt shift of the light–dark cycle to investigate the mechanism underlying phase adjustment of the SCN. Following such a shift, a dissociation of the electrical profiles and the molecular expression patterns of the ventral and dorsal SCN becomes visible (Albus et al., 2005; Davidson et al., 2009; Nagano et al., 2003; Nakamura et al., 2005; Reddy et al., 2002; Yan and Silver, 2004). Desynchrony between the dorsal and ventral SCN areas can also be induced by exposure of rats to short light–dark cycles (de la Iglesia et al., 2004), but in the case of a jet lag, the phase desynchrony is transient and coupling is eventually restored. Following a shifted light–dark cycle, the neurons in the ventral SCN appear to shift rapidly followed by a much slower shift of the dorsal SCN (Albus et al., 2005; Nagano et al., 2003; Nakamura et al., 2005). The difference in phase-resetting speed may relate to the differential innervation of the ventral versus the dorsal SCN area by the retina (Antle and Silver, 2005, 2009; Card et al., 1981; Gamble et al., 2007; van Esseveldt et al., 2000). The ventral SCN receives most of the retinal input (Ibata et al., 1989; Kiss et al., 2008; Morin and Allen, 2006)

and shows more robust light-induced changes in electrical activity (Meijer et al., 1998; Shibata et al., 1984) and gene expression (Dardente et al., 2002; Guido et al., 1999; Karatsoreos et al., 2004; Kuhlman et al., 2003; Schwartz et al., 2000; Yan et al., 1999). The initial shift of the ventral SCN may thus be explainable by the stronger influence of environmental light input on this part of the nucleus.

The rapid shift of the ventral SCN can be easily observed in an SCN slice, prepared after exposure to a 6-h delay of the light–dark cycle (Albus et al., 2005). The differential shifts of ventral and dorsal SCN become visible by two peaks in the multiunit activity rhythm. The one peak is delayed by nearly 6 h, while the other peak shows no significant shift. A surgical cut, made between the ventral and dorsal part, made it clear that the shifted component originates from the ventral part, and the unshifted component from the dorsal part. The findings also show that, in the intact slice, communication and transfer of electrical activity occur within the SCN circuitry, as in intact slices, both components are visible in the dorsal and ventral SCN. The transmittance of information may rely on GABAergic activity as bicuculline blocked the information transfer, and single peaks (i.e., a shifted peak in the ventral SCN and an unshifted peak in the dorsal SCN) were observable in intact slices in the presence of bicuculline.

GABA plays a role in the transfer of information between ventral and dorsal SCN. SCN neurons receive a tonic GABAA receptor-mediated synaptic input that, at least partly, originates within the SCN itself and peaks during the night (Itri et al., 2004; Jiang et al., 1997; Kim and Dudek, 1992; Strecker et al., 1997). Although GABA is normally an inhibitory transmitter within the SCN, for a certain percentage of cells within the SCN circuit, GABA can play an excitatory role in communication (Choi et al., 2008; Irwin and Allen, 2009). This GABA-mediated excitation is critically dependent on the activity of the chloride pump NKCC1 (Belenky et al., 2010; Choi et al., 2008). Recent work in other hypothalamic neurons demonstrates that the activity of NKCC1 can be actively regulated such that GABA can switch from being inhibitory to excitatory as a function of physiological demands (Kim et al., 2011). It is quite possible that a similar dynamic regulation of GABA signaling may be occurring in the SCN. Functionally, the exogenous application of GABA can synchronize the electrical activity of SCN neurons (Liu and Reppert, 2000; Shirakawa et al., 2000), and GABA may synchronize ventral and dorsal SCN following a shifted light cycle (Albus et al., 2005); however, GABAergic signaling does not appear to be required for cultured SCN neurons to remain synchronized (Aton et al., 2006).

It is evident that the shift of the ventral SCN ultimately causes a phase shift of the whole SCN network. When an SCN slice is prepared following the shift of the light–dark cycle, and after three days in constant darkness, the dissociation within the SCN is still observable (Albus et al., 2005; Nagano et al., 2003; Nakamura et al., 2005). After day 6 in constant darkness, the dorsal and ventral SCNs have resynchronized, and the final peak time is near the time of the shifted ventral SCN. These findings indicate a strong effect of the ventral on the dorsal SCN, while, in contrast, the dorsal SCN has a small effect on the ventral SCN. The idea that light information flows from ventral to dorsal is consistent with anatomical studies (Moore et al., 2002; Romijn et al., 1997).

An intriguing observation in our experiments was that the shifted component of the multiunit activity pattern was consistently narrower than the unshifted component (Fig. 5). A curve fitting analysis revealed that this observation was highly consistent (Rohling et al., 2011). We performed recordings of neuronal subpopulations following exposure to the shifted light–dark cycle and observed that only 20% of the neurons peaked in the middle of the new light phase. This indicates that only 20% of the neurons seemed to have shifted on the first day after the shift in the light cycle (Rohling et al., 2011). The narrowness

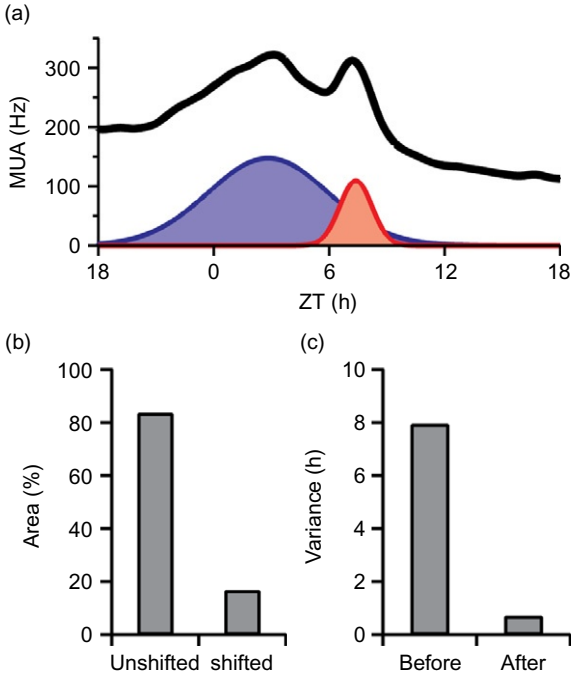

Fig. 5. After a 6-h delay of the LD cycle, one small population of neurons shifts its activity immediately to the new LD regime, while another, larger population of cells remains active in the old phase. (a) Example of a typical bimodal SCN rhythm, following a phase delay (black line). The timescale indicates the new Zeitgeber time, that is, ZT 6 is the middle of the shifted day. When Gaussian functions were fitted through the MUA pattern, two different Gaussian functions were found in this example. One Gaussian function represents an unshifted population and one represents a shifted population. In this example, the percentage of action potentials responsible for the unshifted population is 83%, while the shifted component contains 17% of the action potentials. (b) For all recordings, subpopulation patterns were recorded and the variance between the different phases of the subpopulations was assessed. The subpopulations before the trough, in the unshifted component, had a much larger variability than the subpopulations after the trough, in the shifted component (7.9 vs. 0.7 h, respectively). (c) Our data indicate that the neurons in the shifted component are much more synchronized than the neurons in the unshifted component.

of the peak of the shifted component is not a trivial finding when a low number of subpopulations is recorded, as can be shown by Monte Carlo simulations (Schaap et al., 2003). Instead, it indicates that the shifted neurons are highly synchronized in phase. Recordings of the phase distribution of the shifted neurons confirmed this prediction (Rohling et al., 2011). The percentage of neurons that shifts immediately corresponds with the fraction that shows direct light responsiveness (Meijer et al., 1986) and with the subtype of VIP cells that receive direct retinal input (Kawamoto et al., 2003). These neurons showed an absence of endogenous rhythmicity (Kawamoto et al., 2003), which could make them more susceptible to phase-shifting influence of the light–dark cycle.

From the coupled oscillator theory, we can explain that more tightly synchronized neurons have a bigger influence on less synchronized neurons (Mirollo and Strogatz, 1990; Strogatz, 2003; Winfree, 1967). Thus, when two groups of neurons are out of phase, the more synchronized group will exert a strong phase-shifting effect on the less synchronized group. This can be understood as, in a firmly synchronized population, each neuron is exerting its maximal phase-shifting effect at the same time of the cycle, rendering a strong signal of the group at a particular phase of the cycle. Previous studies reported that the ventral neurons are dominant over the dorsal neurons and determine to a large extent the final phase (Albus et al., 2005; Nagano et al., 2003; Nakamura et al., 2005). The synchronization among the shifted neurons may contribute to their dominance over the unshifted population.

Adjustment to phase advances is more complex than adjustments to phase delays and requires more days. This cannot be explained by the endogenous period of the rhythm, as in nocturnal animals, the period is generally shorter than 24 h, which would facilitate a faster resetting. The slow adaptation to a phase advance results in part from feedback of the central nervous system to the SCN (Vansteensel et al., 2003). In the isolated SCN, when the SCN is deafferented from this feedback input, the phase-advancing capacity is therefore strongly enhanced (Vansteensel et al., 2003).

$Ca_v2.1$ calcium channels play a role in the influence of the central nervous system on the SCN (van Oosterhout et al., 2008). The *CACNA1A* gene encodes the ion-conducting, pore-forming α_{1A} subunit of voltage-gated $Ca_v2.1$ (P/Q type) calcium channels (Ophoff et al., 1996). These channels are predominantly localized at presynaptic nerve terminals in several brain regions (Westenbroek et al., 1995), including the SCN (Chen and van den Pol, 1998; Cloues and Sather, 2003; Nahm et al., 2005), and play a key role in mediating neurotransmitter release (Mintz et al., 1995; Wu et al., 1999). Animals with a gain of function in these channels (used as a migraine model), show enhanced phase-advancing capacity, while their phase delays are unaltered (van Oosterhout et al., 2008). However, the phase-resetting capacity of the SCN in isolation is unaltered in these animals. These findings suggest a role for $Ca_v2.1$ channels in mediating influences of the central nervous system on the SCN, and indeed, the synaptic input to dorsal SCN neurons is enhanced in these animals (van Oosterhout et al., 2008). The complexity of phase advances is thus a consequence of an additional level of organization that attenuates the phase-shifting capacity of the circadian system.

Analysis of the SCN phase synchrony following an advance has shown that also in response to phase advances, the ventral SCN shifts first and is followed by a shift of the dorsal SCN, which is similar to the response to delays (Albus et al., 2005; Nagano et al., 2003; Nakamura et al., 2005; Reddy et al., 2002; Yan and Silver, 2002, 2004). However, advances induce a larger degree of desynchrony within the SCN as compared to phase delays (Rohling et al., 2011). The desynchrony may contribute to the inertia in response to phase advances, and possibly, it is related to the role of the central nervous system in phase advances, as the activation of input pathways from other areas may well contribute to phase desynchrony within the SCN. However, the role of extra SCN areas on the SCN is to date largely unexplored and deserves attention in future studies.

Collectively, the phase-resetting studies lead to the following model for resynchronization: In response to a shifted light cycle, only the oscillators in the ventral SCN are initially shifted. Other areas of the SCN become synchronized to the shifted light cycle through interoscillator-coupling mechanisms. GABA may be involved in the transmission between ventral and dorsal oscillators. The strong effect of the small group of ventral neurons on the dorsal neurons may rely on the excitatory effect of GABA on the dorsal SCN as well as on the high degree of synchrony of the shifted versus the unshifted cells.

The differences in phase synchronization among neuronal populations as observed under light–dark cycles, under constant light, under shifted light cycles, and under changes in photoperiod have made clear that the multioscillator structure of the SCN is strongly involved in the adaptive function of the SCN. The different environmental conditions can lead to reconfiguration of the phases among the SCN population and determine the waveform of the SCN rhythm. These findings are in agreement with the theory of coupled oscillators, which proposes that the same system of coupled neurons can account for many different states just by changing its configuration (Golubitsky et al., 1999; Mirollo and Strogatz, 1990; Strogatz, 2003; Strogatz and Stewart, 1993). These findings also lead to the question of how the coupling among SCN oscillators is affected by aging and diseases.

Effects of aging and disease

Disruptions in the circadian system, including decreased amplitude of rhythmic behaviors and fragmentation of the activity–rest episodes, are commonly associated with aging in humans and other mammals (Carrier and Bliwise, 2003; Van Someren, 2000). While undoubtedly many factors contribute to these changes, a variety of data (Aujard et al., 2001; Biello, 2009; Satinoff et al., 1993; Turek et al., 1995; Watanabe et al., 1995) are emerging that is consistent with the

hypothesis that an age-related decline in the output of the central circadian clock in the SCN may be key. For example, in recent work, *in vivo* multiunit recordings were carried out from the SCN and a brain region that receives robust innervation from the SCN (subparaventricular zone) in freely moving animals. The amplitude of the day–night difference in neural activity was substantially reduced in both brain regions of middle-aged mice (Nakamura et al., 2011). Another striking feature was the increase in variation in the levels of the spontaneous activity. In contrast, the molecular clockwork in the SCN as measured by PERIOD2 levels was not disrupted in middle-aged mice. These results suggest that the age-related disruption in the circadian output occurs before any disruption of the molecular clockwork. The mechanisms underlying the age-related decline in SCN neural activity are unknown but are an important area for future research. As both sleep states (Deboer et al., 2003) and locomotor activity (Meijer et al., 1997; Schaap and Meijer, 2001; Yamazaki et al., 1998) can "feedback" to regulate SCN neural activity, future studies will need to address the issue of to what extent the age-related decline in sleep and activity contributes to the reduced SCN neural activity seen *in vivo*. Several studies have shown that the electrophysiological activity of aged SCN neurons *in vitro* is altered in situations where these feedback mechanisms would not be in operation (Aujard et al., 2001; Biello, 2009; Nygard et al., 2005; Satinoff et al., 1993; Watanabe et al., 1995). The firing rate changes found in the SCN itself could be mediated by age-related alterations in synaptic transmission within the circuit as well as changes in ion mechanisms and cellular metabolism intrinsic to single SCN neurons.

Patients suffering from neurodegenerative disorders including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) commonly exhibit sleep disorders. These patients have difficulty sleeping at night and staying awake during the day. These symptoms have a major impact on the quality of life of the patients and on their caregivers. While the underlying pathology has not yet been identified, several studies have been carried out using mouse models of these neurodegenerative diseases (Kudo et al., 2011a,b; Morton et al., 2005; Oakeshott et al., 2011; Sterniczuk et al., 2010). Most of these mouse models exhibit circadian disruptions and there is at least some evidence that treatments designed to stabilize these rhythms can improve other, non-motor symptoms of these mice (Maywood et al., 2010; Pallier et al., 2007). In one of the mouse models of HD (the BACHD line) in which the mutated human *Htt* gene is expressed, the output of the circadian system as measured by locomotor activity, heart rate, and body temperature was profoundly disrupted early in the life span (Kudo et al., 2011b). The neural activity rhythms in the SCN, but not rhythmic PER2 expression, were also reduced in the BACHD mice. A very similar story is emerging from a study of a line of alpha-synuclein-overexpressing (ASO) mice (Kudo et al., 2011a). Selective deficits were found in the expression of circadian rhythms of locomotor activity, including lower nighttime activity and greater fragmentation in the wheel-running activity in this model of PD and other synucleinopathies. The temporal distribution of sleep was also altered in the ASO mice compared to littermate controls. In the ASO mice, the peak–trough expression of the clock gene PERIOD2 was normal in the SCN; however, the daytime firing rate of SCN neurons was reduced in the mutant mice. Together, these data in mouse models of AD, HD, and PD in combination with the clinical symptoms raise the possibility that a weakening of circadian output is a core feature of neurodegenerative diseases.

Could disease processes alter the synchrony of the SCN circuit?

One mechanism by which aging and disease can alter the function of the circadian system is by reducing the strength of the intercellular coupling within the SCN circuit. Recent work in a variety

of mouse models of neurodevelopmental and psychiatric disorders suggests that alterations in the balance between synaptic excitation and inhibition are at the heart of the pathophysiology in these conditions (Dani et al., 2005; Gogolla et al., 2009; Milnerwood and Raymond, 2010; Nelson and Turrigiano, 2008; Shepherd and Katz, 2011). Within the SCN circuit, glutamate and the peptide PACAP are the neurotransmitters released from the RHT that drive the effects of light on the retinorecipient SCN neurons (Colwell, 2011; Morin and Allen, 2006). For neurons within the circuit, the main transmitter within the SCN is GABA (Moore and Speh, 1993; Okamura et al., 1989) with most neurons receiving a constant flux of GABA signaling (Itri et al., 2004; Jiang et al., 1997; Kim and Dudek, 1992; Strecker et al., 1997). Interestingly, GABA can mediate both inhibitory and excitatory postsynaptic effects within the SCN (Choi et al., 2008; Gribkoff et al., 1999; Irwin and Allen, 2009; Wagner et al., 1997) with the activity of the chloride pump NKCC1 being the critical determinant (Belenky et al., 2010; Choi et al., 2008; Irwin and Allen, 2009). So, one likely consequence of a number of diseases of the central nervous system is a change in the balance between excitation and inhibition synaptic transmission. While we have no specific evidence for a disease that alters synaptic transmission or coupling within the SCN circuit, this remains a very plausible mechanism to explain the disruption in circadian function. Recent work shows that the blockade of synaptic transmission within the SCN disrupts both circadian gene expression and neural activity rhythms (Deery et al., 2009; Kim et al., 2009). In addition, the SCN circuit highly expresses several peptides including VIP, GRP, vasopressin, and PK2. We do not know whether these peptides function as neurotransmitters or more as cofactors within this circuit. Among these peptides, perhaps the best studied is VIP and there is overwhelming evidence for this peptide playing a critical role in coupling or synchronizing cellular oscillators within this circuit (Freeman and Herzog, 2011; Maywood et al., 2011; Vosko et al., 2007; Welsh et al., 2010). A number of studies have found evidence that the levels of VIP in the SCN are reduced with aging and neurodegenerative diseases in humans and rodents (e.g., Duncan et al., 2010; Fahrenkrug et al., 2007; Mazurek et al., 1997; Pereira et al., 2005; Zhou et al., 1995). These data add a key support to our suggestion that an important consequence of disease pathology will be to alter intra-SCN coupling within the circadian circuit and decrease the synchrony of the SCN population. Based on the work described in this chapter, the loss of coupling and decreased synchronization would have the consequence of reducing the phase-shifting effects of light and other phase-shifting agents. The reduced synchrony would also reduce SCN neural activity and, as a consequence, reduce the amplitude of any SCN-driven output. A reduction in output would be expected to change the phase relationships between the SCN and the peripheral oscillators. Thus, many of the key circadian symptoms exhibited with aging and diseases of the nervous system could be explained by a reduction in the synchrony of the SCN cell population.

These types of disruptions of circadian system caused by altered coupling within the SCN circuit are likely to have profound consequences on patient health (Hastings et al., 2003; Reddy and O'Neill, 2010; Takahashi et al., 2008). We believe that robust circadian rhythms are essential to good health. In recent years, a wide range of studies have demonstrated that disruption of the circadian system leads to a cluster of symptoms, including metabolic deficits (Gale et al., 2011; Marcheva et al., 2010; Turek et al., 2005), cardiovascular problems (Bray et al., 2008; Scheer et al., 2009), difficulty sleeping (Reid and Zee, 2009; Wulff et al., 2009), and cognitive deficits (Gerstner et al., 2009; Loh et al., 2010; Wang et al., 2009). Many of these same symptoms are seen in aging and neurodegenerative diseases. This suggests that we should put a greater emphasis on the development of pharmacological tools and behavioral interventions that can boost

neural activity rhythms and the synchrony of the SCN cell population in situations in which the molecular clock may still be working.

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