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The input pathways to the circadian clock: from nocturnality to diurnality

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Citation

Schoonderwoerd, R. A. (2023, May 16). *The input pathways to the circadian clock: from nocturnality to diurnality*. Retrieved from <https://hdl.handle.net/1887/3618376>

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

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General Introduction: Diurnality and the mammalian biological clock network

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Abstract

In the endless contest for survival, life on Earth adapted to function optimally in its own temporal niche: daytime or night-time. The mammalian ancestor, which was exclusively nocturnal, obtained the opportunity to explore diurnality after the mass extinction of the diurnal dinosaurs. However, this temporal niche switch from nocturnality to diurnality required evolutionary alterations in the biological clock, which is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. For many years, researchers have proposed the existence of a simple switch mechanism for temporal niche preference, somewhere downstream from the biological clock. We hypothesize that a single diurnality switch does not exist. Rather, factors in all four functional components of the biological clock (i.e. its input, the SCN network, output and feedback into the biological clock) contribute to some extent to diurnality. For instance, differences between diurnal and nocturnal species are reported in the percentage of light suppressed SCN cells (input), behavioural responses to constant conditions (SCN network), SCN downstream target neurons (output) and the effect of behavioural activity on SCN electrical activity (feedback). In order to attain a diurnal activity pattern, descendants of the nocturnal mammalian ancestor had to alter as many diurnality influencing traits in these four functional components as possible. Because diurnality evolved several times independently in mammalian history, the mechanisms underlying diurnality may vary among diurnal species. This is a crucial insight to keep in mind in future diurnality research, which will remain essential for the translation of research findings in nocturnal rodents to the diurnal humans.

Keywords: Diurnality, suprachiasmatic nucleus, circadian rhythms, temporal niche switching, nocturnal bottleneck

Abbreviations

AVP	Arginine vasopressin
GABA	γ -aminobutyric acid
GHT	Geniculohypothalamic tract
GnRH	Gonadotropin-releasing hormone
GRP	Gastrin-releasing peptide
IGL	Intergeniculate leaflet
ipRGC	Intrinsically photosensitive retinal ganglion cell
LD cycle	Light/dark cycle
NPY	Neuropeptide Y
PRC	Phase response curve
RHT	Retinohypothalamic tract
SCN	Suprachiasmatic nucleus

SPVZ	Subparaventricular zone
VIP	Vasoactive intestinal peptide

1. Introduction

Many organisms possess an internal clock based on terrestrial day length, to anticipate the fluctuating environmental conditions caused by the revolution of the Earth, such as environmental light, food availability, the presence of predators and ambient temperature (1–4). Using this biological clock, mammals are able to maintain circadian (5–10) (“circadian”, approximately a day) and seasonal (11–13) rhythms in physiology and behaviour. These endogenous 24-hour rhythms are carefully aligned to the environment (entrained) with light as the predominant synchronization cue (7, 14–16). Although all organisms have rhythms with a 24-hour period, the phase of the circadian rhythms varies per species, some being active during daytime (diurnal), others during the night (nocturnal). The exact underlying mechanisms for diurnality and nocturnality remain unresolved (17).

Most biomedical research into the biological clock is performed in nocturnal laboratory animals. However, in order to translate these findings to the diurnal humans, comparison of diurnal and nocturnal species is essential. The biological clock relies heavily on interneuronal communication and networks. Therefore, this chapter aims to elucidate the neuronal network differences between diurnal and nocturnal mammals. The four functional components of the biological clock are (i) input from the retina to synchronize its rhythm to the environment, (ii) a network structure to maintain synchronous pacemaker activity even when deprived from external cues, (iii) output mechanisms to regulate physiological and behavioural rhythms in the body and (iv) feedback into the biological clock to reintegrate the outputs of the circadian system (Figure 1). We will chapter these four components in this article, with a special focus on the SCN network, in order to summarize the present understanding of diurnality, to identify gaps in this knowledge and to propose directions for future research.

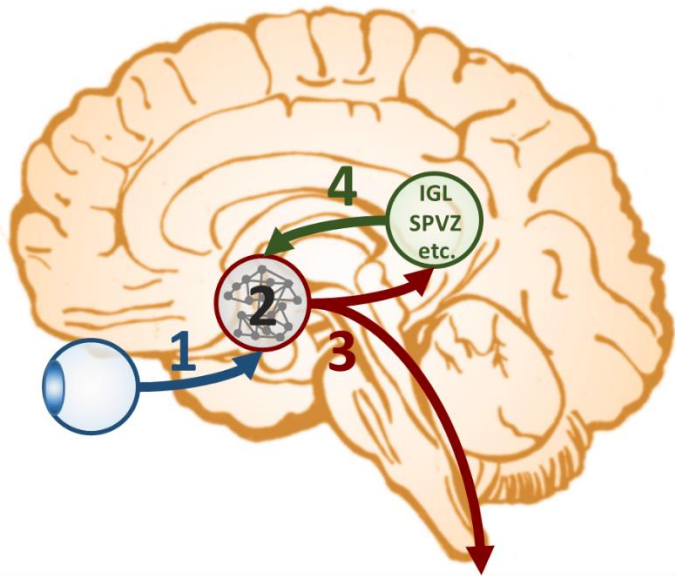


Figure 1: The four functional components of the biological clock. The biological clock requires (i) light input from the retina, (ii) a network structure within the suprachiasmatic nucleus (SCN) to maintain synchronous pacemaker activity, (iii) output pathways to the rest of the body and other brain regions, among which the intergeniculate leaflet (IGL) and subparaventricular zone (SPVZ), and (iv) feedback of other brain regions back into the SCN. We hypothesize that differences between diurnal and nocturnal species occur in all four functional components.

2. Diurnality

Mammals can be categorized according to their temporal niche: night active mammals are nocturnal and day active animals are diurnally active (17). However, not only locomotor activity patterns differ for nocturnal and diurnal animals. The entire physiology, evidently including sleep timing (18–20), is adapted to the temporal niche under control of the biological clock (21). For example, body temperature shows diurnal fluctuations, peaking in the night for nocturnal animals and during daytime for diurnal animals (22–26). Additionally, nocturnal and diurnal species have a different timing of the glucocorticoid peak, both occurring before the beginning of their respective activity phase (27–30). Despite the anti-phases of body temperature and glucocorticoid rhythms, melatonin peaks during the night for both diurnal and nocturnal mammals (21, 31–33).

All present-day mammals are assumed to originate from a common nocturnal ancestor, also referred to as the “nocturnal bottleneck hypothesis” (34–36). In the Mesozoic era, these primordial mammals experienced fierce competition with the dinosaurs. In order to avoid being predated upon by these predominantly ectothermic diurnal reptiles, mammalian nocturnality was promoted (37). Evidence for this nocturnal bottleneck hypothesis is for example loss of photoreceptor types (38) and UV protection mechanisms in mammals compared to non-mammalian species (39), both due to the decreased light

exposure in the nocturnal niche. After the mass extinction of the dinosaurs, some mammalian species reoccupied the diurnal niche (37). Diurnality evolved in different mammalian lineages independently, indicating that the biological mechanisms of diurnality may vary (40, 41).

Despite humans being diurnal, nocturnal rodents, such as rats (*Rattus norvegicus*) (42, 43), mice (*Mus musculus*) (44, 45) and hamsters (*Mesocricetus auratus*) (46) are the most common animal models used in chronobiology research. In these species, more than 94% of the locomotor activity occurs in the dark phase, with an activity peak closely after light offset (47). Although to a considerably lesser extent, several diurnal rodents are also used. Studies have been published on the degu (*Octodon degus*) (48–50), Nile grass rat (*Arvicanthis niloticus*) (23, 51, 52), Sudanian grass rat (*Arvicanthis ansorgei*) (53–55), ground squirrel (*Spermophilus citellus*) (56, 57) and tree shrew (*Tupaia belangeri*) (58–60) amongst others (Table 1). While most of the locomotor activity in these rodents occurs in the light phase, some individual animals show crepuscular rhythms, with a bimodal activity profile peaking around dawn and dusk, suggesting a gradual nature of diurnality (47, 61).

Table 1: Diurnal laboratory animals

Species	English name	Reference
<i>Acomys russatus</i>	Golden spiny mouse*	Cohen <i>et al.</i> 2006, 2009 (62, 63)
<i>Ammospermophilus leucurus</i>	White-tailed antelope squirrel	Pohl <i>et al.</i> 1983 (64)
<i>Arvicanthis ansorgei</i>	Sudanian grass rat	Challet <i>et al.</i> 2002 (54)
<i>Arvicanthis niloticus</i>	Nile grass rat	Katona <i>et al.</i> 1997 (51)
<i>Ctenomys</i> aff. <i>knightsi</i>	Catamarca tuco-tuco	Flôres <i>et al.</i> 2013 (65)
<i>Eutamias sibiricus</i>	Siberian chipmunk	Sato & Kawamura 1984 (66)
<i>Funambulus palmarum</i>	Palm squirrel	Navaneethakannan <i>et al.</i> 1986 (67)
<i>Lemniscomys barbarus</i>	Barbary striped grass mouse	Lahmam <i>et al.</i> 2008 (68)
<i>Meriones unguiculatus</i>	Mongolian gerbils [#]	Weinert <i>et al.</i> 2007 (69)
<i>Octodon degus</i>	Degu [#]	Lee & Labyak 1997 (48)
<i>Psammomys obesus</i>	Fat sand rat	Barak <i>et al.</i> 2013 (70)
<i>Rhabdomys pumilio</i>	Four-striped field mouse	Schumann <i>et al.</i> 2005 (71)
<i>Spermophilus citellus</i>	European ground squirrel	Hut <i>et al.</i> 1999 (56)
<i>Spermophilus tridecemlineatus</i>	Thirteen-lined ground squirrel	Meijer <i>et al.</i> 1989 (72)
<i>Tamias striatus</i>	Eastern chipmunk	Kramm <i>et al.</i> 1980 (73)
<i>Tupaia belangeri</i>	Tree shrew	Meijer <i>et al.</i> 1990 (60)

*Only diurnal in the presence of its natural competitor *Acomys cahirinus* (74). [#]Sometimes considered crepuscular or nocturnal due to interindividual variability (22, 47).

This view is supported by observations on temporal niche switching upon environmental alterations, such as hypocaloric feeding (75), cold exposure (76), social interactions (77, 78), a transfer from natural environments to a laboratory (79, 80) or access to a running wheel (52, 80–82). Even differences in diurnality between individuals of the same species occur (47, 81). The current theory on temporal niche switching in an individual's life span, is the hypothesis of circadian thermoenergetics (39). According to this hypothesis, organisms choose their temporal niche by taking energy balance, survival and reproduction into account. Based on energy balance, diurnality would be the most favourable temporal niche for endothermic mammals (39, 83). Therefore, in times of a negative energy balance, for instance food shortage, nocturnal animals resort to diurnality (84). Whether the mechanisms underlying temporal niche switching on the ecological level are similar to the evolutionary timescales, remains an interesting question (85).

3. The mammalian biological clock

Mammalian diurnality and circadian rhythmicity are regulated by the biological clock, located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus in both the nocturnal (86, 87) and diurnal mammalian brain (66, 88). SCN electrical and metabolic activity follow a sinusoidal pattern and peak during the middle of the light period (89, 90). Interestingly, the electrical (66, 91, 92) and metabolic activity rhythms (93, 94) of the SCN are similarly phased for diurnal and nocturnal animals, despite the difference in behavioural activity phase.

The circadian SCN rhythm results from the cumulative activity of the approximately 20,000 synchronized single neuron oscillators with a circadian rhythm (89, 95–100). SCN activity remains rhythmic when isolated in vitro (90, 101, 102), demonstrating its intrinsic circadian pacemaker activity. The intrinsic circadian rhythmicity of single SCN neurons results from molecular transcriptional-translational positive and negative autoregulatory feedback loops, leading to fluctuating levels of clock gene (e.g. *CLOCK*, *BMAL*, *PER*) transcription (1, 103–106). Despite reports on subtle differences in clock gene expression (107, 108), the clock genes are generally equally phased (109–112) and respond similarly to photic stimuli in diurnal and nocturnal species (111, 113–115). The overall similarity in clock gene expression implies that most differences between diurnal and nocturnal animals are located elsewhere than within the individual oscillating SCN neurons. Therefore, this chapter will focus on network properties and neuronal communication of the biological clock rather than the intracellular transcriptional-translational feedback loops.

4. Photic input into the circadian system

Ambient illuminance input into the circadian system is essential in order to synchronize the internal rhythm to external light-dark cycles (16, 116, 117). The SCN receives direct

retinal glutamatergic input via the retinohypothalamic tract (RHT) (14, 118–120), independently of the pathways for pattern recognition (121–124). At the basis of the RHT are retinal ganglion cells, most of which are intrinsically photosensitive (ipRGCs) (125–128). ipRGCs contain the photopigment melanopsin (123, 128–131), and receive synaptic input from the classical photoreceptors, rods and cones (132–140), which contain the photopigments rhodopsin and iodopsin, respectively (141). All photoreceptors were first observed in nocturnal animals and were confirmed to be similar in diurnal species, including humans (130, 131, 142–144), which also possess melanopsin-containing ipRGCs with similar projection pathways (145–148). The indirect light input pathway from the intergeniculate leaflet (IGL) via the geniculohypothalamic tract (GHT) is also comparable in diurnal and nocturnal mammals (147, 149–151). Thus, no prominent differences in the structural anatomy of the visual input pathways to the biological clock have been found between diurnal and nocturnal species.

Nocturnal and diurnal mammal species show however some differences in visual systems in order to adapt to their temporal niches optimally (36, 37, 152–154). Eyes of nocturnal species are relatively large, with enlarged cornea (155), more overlap in ocular fields (36) and even with a different localization of heterochromatin in the nuclei of rods functioning as lenses (156), all to improve light sensitivity. Furthermore, nocturnal animal retinas generally have a lower cone percentage than diurnal species, because cone photoreceptors require higher light intensities than the intensities reached during the night (39, 152, 157). To improve light sensitivity further, more photoreceptor cells converge on a single retinal ganglion cell in nocturnal species compared to diurnal species, at the cost of visual acuity (158). This results in diurnal species having thicker optic nerves, to transmit the information from the larger number of retinal ganglion cells to the visual brain areas (118, 147, 159–161). Additionally, diurnal species are exposed to higher levels of DNA damaging short-wavelength light during daytime and therefore require spectral filtering. This is accomplished by UV absorbing compounds in the lens (162, 163) and aqueous humour (164). Nocturnal species generally lack these UV filtering properties, which allows possession and use of short-wavelength cones maximally sensitive to UV light (37).

Compared to nocturnal species, diurnal species generally have cone enriched retinas and therefore suffer from limited cone function in night irradiance levels (132, 165, 166). Studies in mammals show that diurnal retinas contain more cones and cone types than nocturnal retinas (39, 157, 167). While in nocturnal mice and rats only approximately 3% (168, 169) and 1% (170, 171) of the photoreceptors are cones, respectively, diurnal Sudanian and Nile grass rats and Barbary striped grass mouse (*Lemniscomys barbarous*) have roughly 33% cones (172–174), up to 95% in diurnal ground squirrels (175) and tree shrews (176). Nevertheless, whereas all nocturnal species generally have low cone percentages, diurnal species are more variable in cone percentages. In diurnal humans for

example, only 5% of the photoreceptors are cones (177), which argues for careful translation of animal research to humans.

Although a stronger cone input is indeed observed in the electroretinograms of ipRGCs in diurnal Sudanian grass rats (146, 178), the consequences of this different retinal composition for circadian rhythmicity have not been elucidated yet. Human and mouse studies on cone photoreceptor input into the biological clock, suggest that cones are mediating fast transient responses to light, thereby encoding light transitions (179–184). Increased light transition sensitivity in diurnal species would be convenient for entrainment, as light transitions are often experienced by diurnal animals, because of their dynamic locomotor activity during the light period. Furthermore, cones are found to convey information on the wavelength of light to the SCN (185–187). Consequently, diurnal mammals may be more sensitive to dawn and dusk, which are characterized by changing spectral compositions of light (185, 187, 188).

It is also well established that cones are less sensitive to light than rods. Cone sensitivity starts from 10.7 log photons/cm²/s (132, 165), with a reported range of 6–7 log units (166), while rods are sensitive to irradiances down to 6.5 log photons/cm²/s (165, 182). This corresponds to findings that diurnal circadian systems seem less sensitive to light. The light intensity threshold for phase shifting in nocturnal hamsters is approximately 11 log photons/cm²/s (46) or 0.1 lux (122, 189), which is already fairly high compared to the thresholds for conscious vision. In diurnal species, this threshold was even higher, amounting roughly 200 lux in humans (190, 191) and diurnal tree shrews (60). Additionally, diurnal species generally require light pulses of longer duration for phase shifting than nocturnal species (7, 60, 117, 189, 192). Careful interpretation is however required, as this difference in light sensitivity may also be attributed to previous lighting history (193).

A role of photoreceptors in temporal niche preference is also found in knockout models of nocturnal mice. Interestingly, melanopsin knockout (*Opn4*^{-/-}) mice are more likely to exhibit diurnal activity patterns than the predominantly nocturnal wildtype mice (194, 195). Even more striking, “cone-only” mice, lacking both melanopsin and rods (*Opn4*^{-/-} *Gnat1*^{-/-}), show a strong tendency for diurnality, with merely 37.6% of the total locomotor activity occurred in the dark (194).

Further evidence of retinal mutations influencing diurnality is provided by Doyle *et al.* in a study on mice lacking melanopsin and cone functionality and having only partly retained rod functionality (*Opn4*^{-/-} *Rpe65*^{-/-}). In this study, a vast majority (~80%) of mice turned diurnal, while the remaining 20% free-ran (196). This diurnality was complemented by clock gene phase reversal in the SCN and reversal of the masking response (197), which is the acute behavioural response to light (4, 198–202). This indicates that temporal niche preference can theoretically be reversed by alterations located upstream of the SCN (197), presumably involving the retinal light signalling network of bipolar, amacrine and retinal

ganglion cells (203). Additionally, wildtype mice on a light/dark (LD) cycle with dim light exhibited similar diurnal patterns as the *Opn4^{-/-}Rpe65^{-/-}* mice (197). The reason for this similarity is presumably that *Opn4^{-/-}Rpe65^{-/-}* mice perceive bright light as dim light as well because of their photoreceptor loss. The preference for dim light rather than complete darkness (204) corresponds to positive masking in dim light conditions found in mice (199).

Also, the fraction of light responsive SCN neurons is different between diurnal and nocturnal species, which is a finding that has been rather neglected. In nocturnal rats, mice and hamsters, the percentage of light responsive SCN neurons is approximately 30% (183, 205–207), while in diurnal ground squirrels and degus only 10-25% of the SCN neurons is light responsive (72, 206). It should however be noticed that the amount of light responsive cells can vary considerably during the day (208).

These light responsive SCN cells can either be excited or suppressed in response to light (135, 183, 207, 209–211). In nocturnal rats, mice and hamsters, the vast majority of the light responsive SCN neurons were excited by light (~80%) (183, 205, 206, 208, 212), while in diurnal ground squirrels and degus on average only one third of the cells was light excited, the remainder being suppressed by light (72, 206). As a result, the percentages of light suppressed SCN neurons in diurnal rodents resemble those of nocturnal rodents, however, diurnal rodents possess fewer light excited neurons.

The suppressive light responses are presumably γ -aminobutyric acid (GABA) dependent (213), which is released from a small percentage of GABA containing ipRGCs fibers (214). This means that between diurnal and nocturnal species, there may either be differences in (i) GABA and glutamate release from the RHT, (ii) in the abundance of their receptors on SCN neurons or (iii) in the presence of interneurons modifying the light input signal of the ipRGCs. Consistent with the second, are the different vulnerabilities found to the excitotoxic drug N-methyl-D,L-aspartic acid between diurnal Nile grass rats and nocturnal hamsters (215, 216).

In summary, the input pathways are generally similar between diurnal and nocturnal species. Still, the diurnality observed in nocturnal mice upon photoreceptor ablation shows that temporal niche preference can theoretically be influenced by the input pathways (196, 197). However, this resulted in reversed clock gene expression patterns in the SCN, while SCN clock gene phasing is not reversed in diurnal and nocturnal species (109–112). Thus, there is no evidence of such mechanism occurring naturally to promote diurnality in mammals (41). Nonetheless, considering the higher cone percentages in the retinas of diurnal species (39), and different responsivity of SCN neurons to light (72, 206), we suggest that a difference in photic input between diurnal and nocturnal species is certainly present. Future research should evaluate to what extent this difference influences diurnality.

5. SCN network

The second functional component of the circadian system is the SCN network. Even though single SCN neurons exhibit circadian firing rhythms (95–98), the unique SCN network organization enables synchronization of the individual neuronal rhythms (217–220), in order to generate a cohesive output rhythm (96, 217, 221–224). The SCN network synchronization is accomplished by a complex interplay of various neuropeptides (225), allowing the network to shift its phase and preserve rhythmicity if an organism is maintained in constant conditions (4, 7). Additionally, the SCN network organization provides the ability to adapt to different photoperiods by adjusting the synchronization state (226–228). In this section we will evaluate how these aspects of the SCN network differ between diurnal and nocturnal species.

5.1 Neuropeptides

Neuronal synchronization of SCN neurons can be achieved by electrical coupling through gap junctions (229–232) and chemically via neurotransmitters and neuropeptides (233–239), such as GABA (240–243), vasoactive intestinal peptide (VIP) (235, 244, 245), gastrin-releasing peptide (GRP) (246, 247) and arginine vasopressin (AVP) (248). The SCN can be divided in the ventrolateral core region and the dorsomedial shell region (237, 249). The SCN core contains neurons expressing GRP (246, 247) and VIP (250, 251), and receives visual and non-visual inputs (120, 252, 253). VIP has an important role in mediating responses to ambient light (254–256), circadian rhythmicity and synchrony in the SCN (244, 257, 258), whereas GRP released from SCN neurons is involved in the processing of photic signals to mediate photoentrainment, by increasing excitability of SCN neurons for multiple hours (246, 247, 259, 260). AVP neurons are mostly located in the shell (120), which is believed to contain the intrinsic pacemaker functionality (261–263) and synchronizes the phase of the peripheral clocks in the body (264–266). AVP expression in the SCN is rhythmic and AVP transcription is directly regulated by the CLOCK/BMAL1 heterodimers (267). AVP neurons in the SCN play an important role in interneuronal coupling, thereby providing stability to the circadian clock (268, 269). GABA is expressed in a large majority of the SCN neurons, both in the core and the shell (120). It is involved in interneuronal coupling in the SCN (242, 243, 270) and connecting the core with the shell (240).

Generally, similarities are found between neurotransmitter and neuropeptide localization and SCN subdivisions in diurnal and nocturnal species (147, 160, 271, 272). However, some differences were reported in neuropeptide expression profiles of nocturnal mice and diurnal Sudanian grass rats. When mice and grass rats are on a LD cycle, AVP, VIP and GRP are generally found to be rhythmically expressed (273, 274), with similar peak times in the two species. However, Dardente *et al.* found that VIP and GRP expression in diurnal grass rats phase shifted to peak earlier upon exposure to constant darkness, while in mice

in constant darkness the expression profiles were unaffected (274). In a similar vein, the phase relation between VIP and AVP expression is different in the diurnal three striped South Indian palm squirrel (*Funambulus palmarum*) compared to nocturnal rats (159). Both studies show subtler alterations in circadian neuropeptide organization than a complete reversal, which opposes the view of a single diurnality switch (159, 274). However, we recommend careful interpretation of circadian neuropeptide profiles, because differences between mice and rats, two nocturnal species, are also found (274, 275). Furthermore, differences in VIP expression peaks are also found between male and female diurnal grass rats (276, 277). Moreover, in diurnal humans VIP is not fluctuating (278), which obstructs direct extrapolation of these results further. Therefore, neuropeptide expression profiles demand additional investigation in multiple diurnal species before ascribing these findings to diurnality.

Another dissimilarity in SCN neurotransmitter organization between diurnal and nocturnal mammals has been identified in response to light pulses. Light pulses during the dark period induce the expression of Fos, a transcription factor that can be used as a marker for neuronal activation, in the SCN core of both diurnal and nocturnal species (279–284). The circadian and photic regulation of Fos expression in the SCN are similar for diurnal and nocturnal mammals, both peaking during the subjective day and having highest sensitivity to light pulses during the night (279, 280, 285–288). Nonetheless, Katona *et al.* reported a notable difference between diurnal and nocturnal animals in Fos localization. In diurnal Nile grass rats, Fos is expressed in AVP cells rather than GRP cells, while the opposite applies to nocturnal species (285, 289–291).

Approximately 40% of the GRP expressing SCN neurons in nocturnal rats (289, 290), and 70% of GRP neurons in mice express Fos after a light pulse (291), whereas Fos expression in diurnal grass rat GRP cells is uncommon (285). GRP neurons in the SCN receive direct retinal input in nocturnal species (253, 291, 292), which is consistent with the Fos expression found in GRP neurons of nocturnal rodents (289, 291). In accordance, in nocturnal hamsters *in vivo* release of GRP is affected by light or glutamate agonist N-methyl-D,L-aspartic acid, while AVP is unaffected (293). On the other hand, in rat AVP neurons Fos is virtually absent (281, 290, 294, 295), but expressed in 30% of AVP neurons in grass rats (285). This difference can either result from direct retinal projections to AVP neurons in diurnal grass rats, which are absent in nocturnal rats, or from functional differences in AVP neuron responses to input (294). Although this difference in Fos localization in diurnal Nile grass rats and nocturnal rats is remarkable, it is unknown how it contributes to diurnality (285). Furthermore, it should be kept in mind that this conclusion is only based on observations in grass rats. Extrapolation of these results requires observations from additional diurnal species.

Interestingly, diurnal Nile grass rats and nocturnal rats also appear to differ in the percentage of Fos expressing calbindin cells. Fewer than 1% of calbindin SCN neurons

expressed Fos in grass rats, while in rats 13-17% did (296). Furthermore, intraspecies differences in Fos expressing calbindin neurons are found between diurnal and nocturnal individuals of Nile grass rats in the subparaventricular zone (SPVZ) (296), an output region of the SCN which we will discuss later.

All examples of differences in neuropeptide organization found between diurnal and nocturnal species highlight that the SCN is not a homogenous structure, but rather consists of several cellular subpopulations (274, 285). Thus, the similarities in electrical, metabolic and gene expression rhythms between the entire nocturnal and diurnal SCN do not exclude that differences in subpopulations are present and may contribute to diurnality. Presently, the heterogeneity of the SCN is well acknowledged through the identification of various oscillating subpopulations (9, 297–306). At least four groups of SCN neurons with different phases in circadian activity have been identified, which may represent subnetworks or specific outputs of the SCN (297, 301, 307). It is also reported that some subpopulations are coupled to onset and offset of the activity phase (11, 298, 299).

Subpopulations can be distinguished according to neuropeptide expression, however there may still be heterogeneity within SCN neurons expressing the same neuropeptides. For example, although Fos expression was observed in 40% of GRP neurons in nocturnal rodents and 30% of AVP neurons in diurnal rodents, no Fos expression occurred in the remaining 60% GRP neurons and 70% AVP neurons, respectively (285). Moreover, while 40% of the GRP neurons express Fos, only 10% of Fos expressing cells are GRP neurons (289). Consequently, if the functionality of active subpopulations is reversed, a difference in diurnality can theoretically be accomplished, despite the whole SCN of diurnal and nocturnal species still being active at the same time.

5.2 Phase shifting

In response to light exposure during the dark period, mammals adjust the phase and period length of their behavioural circadian rhythm. These mechanisms form the key ingredient for entrainment to a LD cycle (7, 117, 308–310). Although other stimuli, such as social interactions (311), melatonin administration (312) or access to a running wheel (57), are known to induce phase shifts or cause entrainment, photic input is the most potent mediator (15, 198). The influence of a light pulse on circadian phase depends on its circadian timing (117), intensity (46) and duration (313). Phase response curves (PRCs) show that light pulses in the early or late subjective night cause phase delays or advances, respectively, both in nocturnal (7, 314) and diurnal species (48, 67, 68, 315–318). A minor difference between the PRCs of nocturnal and some diurnal species is the presence of a light unresponsive period, or “dead zone”, during the subjective day. While nocturnal PRCs are insensitive to light during the subjective day, PRCs of diurnal species, including humans (319, 320), remain light sensitive (7, 48, 67, 68, 314, 317, 318). Nevertheless, in

some diurnal species, such as the Nile grass rat and the Sudanian grass rat a dead zone is present in the PRC (315, 316). We presume that the PRCs of diurnal species are more variable than those of nocturnal species, because diurnality evolved in different species independently, suggesting different mechanisms of diurnality (17, 40). It should however be noted that the absence of a dead zone might be an artefact resulting from exposure to light pulses with a longer duration (44).

The period length response curves of diurnal rodents were found to have a similar shape compared to PRCs (44, 310, 318, 321, 322). Period length response curves are, however, more pronounced in diurnal rather than nocturnal species (308, 323), which might also indicate fundamental differences in the SCN network functioning, adapted to the more variable light environment diurnal mammals are exposed to (308).

Similar to light pulses in the dark period, dark pulses during the light period can also induce phase shifts (324). Opposite to the light PRCs, diurnal and nocturnal species have a different sensitivity window to dark pulses. Nocturnal hamsters, diurnal grass rats and diurnal degus have the largest sensitivity during their resting phase, that is the subjective day for nocturnal and subjective night for diurnal species (21, 48, 325). While dark pulse-induced phase shifting is potentiated by serotonergic signalling (326, 327), the exact mechanisms remain to be investigated.

5.3 Constant conditions

Diurnal and nocturnal animals are also found to differ in their behavioural activity pattern response to continuous conditions (4, 328, 329). Upon exposure to constant light, mammals can either (i) remain rhythmic, (ii) become arrhythmic or (iii) show splitting of the behavioural activity pattern (Figure 2) (330). In the cases of remaining rhythmic, Aschoff proposed the hypothesis that in constant light nocturnal species increase period length (τ) and decrease activity phase (α/ρ ratio) with increasing light intensities, whereas the contrary applies to diurnal species (4, 9, 328, 329, 331). While these statements generally hold true for nocturnal species, many exceptions to these rules have been identified for diurnal species (48, 54, 285, 331). Some examples of diurnal rodents not following Aschoff's rule are the fat sand rat (70), golden spiny mouse (62) and four-striped field mouse (*Rhabdomys pumilio*) (71).

Additionally, according to Refinetti, rhythm robustness is affected differently for diurnal and nocturnal species in constant conditions. Upon transition from an LD cycle to constant darkness, the diurnal Nile grass rat loses rhythm robustness while in constant light the rhythm robustness is undisturbed (332). On the other hand, nocturnal hamsters, rats and mice are disturbed by constant light and not so much by constant darkness (330, 332, 333). This effect does not reflect function loss of the biological clock itself, as returning to constant darkness restores the rhythm robustness instantly (332). Generally, nocturnal species have a higher rhythm robustness than diurnal species in normal LD cycles (47), and

unlike nocturnal species, diurnal species are more ambiguous in temporal niche preference (47, 52, 62, 63, 70, 334, 335). Complete arrhythmicity is also observed in constant light conditions, resulting from neuronal phase desynchronization rather than loss of oscillating capacities (330).

Although constant light can induce arrhythmicity, circadian rhythm splitting is also observed in several mammalian species. Upon long-term exposure to constant light, animals exhibit bimodal stably coupled activity phases in approximately 180° antiphase (9, 11, 59). In addition to a split locomotor activity pattern, these animals display split drinking behaviour (336), body temperature (337) endocrine function (338) and SCN electrical activity (339, 340). In nocturnal hamsters (11, 336) and rats (341) bright continuous light induces splitting, while in diurnal ground squirrels (342, 343) and tree shrews (58–60) splitting is induced by constant dim light or even constant darkness (51, 59). Consistent with the different light intensities that induce splitting, are the different light intensities enabling refusion of a split rhythm. Nocturnal species require reduction of light intensity for rhythm refusion (11, 341), whereas diurnal species require bright light (60). Another difference between behaviourally split diurnal and nocturnal mammals is the period of their split rhythm compared to their intact rhythm. In nocturnal species the period length of the split rhythm is generally shorter than the intact rhythm, whereas in diurnal animals the opposite is true (9, 58, 60, 342).

The neurological basis of rhythm splitting has been appointed to the left and right SCN oscillating in antiphase (330, 344). Unilateral SCN lesions correspondingly terminate splitting and generate single activity rhythms (345). Moreover, in hamsters the core and shell of each SCN are found to be in antiphase as well in behaviourally split animals, meaning that the core of one SCN is in phase with the shell of the contralateral SCN (346, 347). There might however be other mechanisms underlying splitting, as some hamsters with unilateral SCN lesions still show splitting (348). Presumably, splitting is the result of alterations of neuronal coupling induced by constant bright light or constant dim light in nocturnal and diurnal animals, respectively (349–351), which may explain why splitting induction is facilitated by preceding splitting (352). However, the coupling mechanisms, which are differently involved in splitting in diurnal and nocturnal species, are still inadequately researched (353).

We can interpret these observations on rhythm robustness and splitting as light having a desynchronizing effect on nocturnal species, whereas in diurnal species darkness seems to be a desynchronizing factor. Considering the arrhythmicity or splitting in bright constant light discussed above (11, 330, 332), evidence on neuronal desynchronization in the SCN of nocturnal species is numerous. Conversely, while some findings support this hypothesis already (59, 332), the potential desynchronizing effect of darkness, or synchronizing effect of light, for diurnal species demands further investigation.

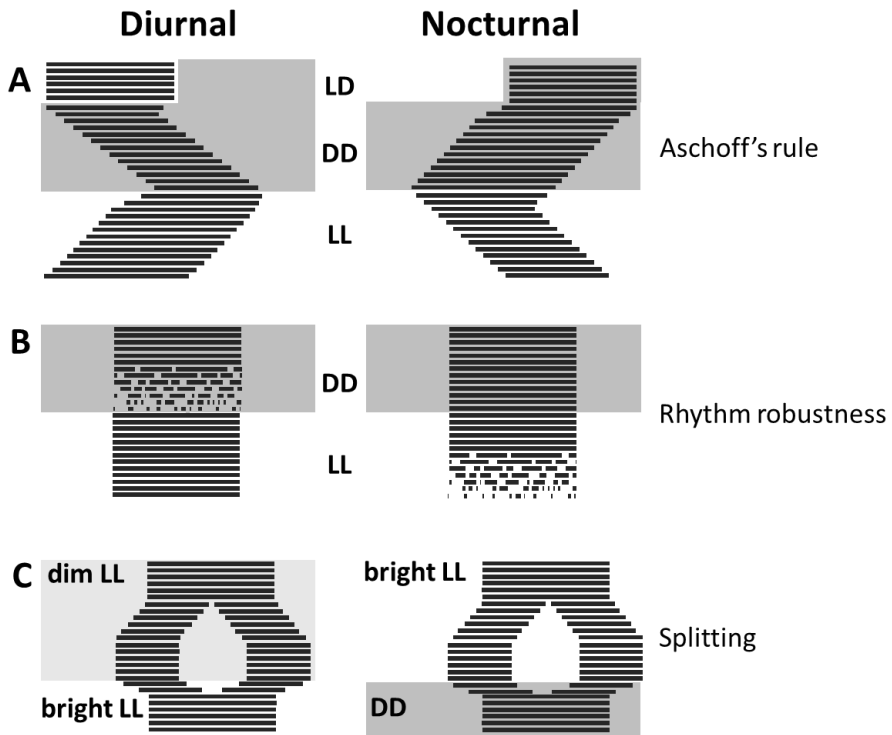


Figure 2: Diurnality in constant conditions. Diurnal and nocturnal species have different behavioural responses to constant conditions. This figure shows three distinct behaviours in constant conditions for diurnal and nocturnal species in schematically represented single plotted actograms. (A) According to Aschoff's rule, diurnal and nocturnal species differ in their period length and activity phase in constant light and darkness. (B) Rhythm disintegration occurs for diurnal species upon exposure to extended periods of constant darkness, while for nocturnal species in constant light. (C) Splitting of the behavioural rhythm occurs in dim constant light for diurnal and bright constant light for nocturnal species, with refusion also occurring in different light regimes. (LD = light/dark cycle; DD = constant darkness; LL = constant light).

5.4 Seasonal adaptation

An approach to study SCN synchronization is via modulation of photoperiods (225, 353). In nocturnal rodents, the SCN electrical activity peak is found to broaden under long photoperiods and narrow in short photoperiod (12, 304, 354). The broad peak in long photoperiods reflects less phase synchrony of the individual neuron oscillators, while the narrow peak in short photoperiods reflects more phase synchrony (227, 228). In accordance, the phase shifts observed in short photoperiods are larger, because light generates larger phase shifts in more synchronized networks (225, 355, 356).

Whether diurnal animals form the mirror image of nocturnal animals concerning photoperiod adaptation, has not been elucidated yet. According to the hypothesis that constant light synchronizes diurnal SCN neurons, the expected outcome would be a

narrow electrical activity peak in long photoperiods and a broad peak in short photoperiods. Instead, no significant differences were found in SCN electrical peak width between short and long photoperiod in diurnal Sudanian grass rats (357). A possible consequence of this observation is that diurnal grass rats show impaired activity phase constriction in short photoperiods (357, 358).

In conclusion, although the metabolic, electrical and clock gene expression rhythms of the SCN in its entirety are similar between diurnal and nocturnal species (66, 91, 93, 109, 111, 114), differences in neuropeptide organization in the SCN on the neuronal subpopulation level are present (274, 285). This heterogeneity of the SCN neurons has been erroneously neglected in diurnality research. Furthermore, the different network properties in diurnal relative to nocturnal mammals become apparent by the dissimilar responses of the SCN network to constant light (60, 332). All these findings give us reason to believe that light input is differently processed in the SCN networks of diurnal and nocturnal species, which may be another crucial factor influencing diurnality.

6. Circadian output

The third functional component of the circadian system is the output, which allows the SCN to exert its function as a central circadian pacemaker. The SCN possesses several efferent pathways to predominantly hypothalamic regions, in order to convey rhythmicity in physiology and behaviour in the whole body (266, 359, 360). To enable regulation of different output rhythms separately (301, 361, 362), various output signals are released from the SCN, among which AVP (120, 363–365), GABA (366–368), VIP (120, 369), glutamate (368), prokineticin-2 (370, 371), TGF- α (372, 373) and cardiotrophin-like cytokine (374). While the exact functions of these signalling factors remain to be elucidated, they are generally secreted during the same circadian phases for diurnal and nocturnal species (276, 375–378).

It is tempting to hypothesize that diurnality is regulated downstream from the SCN (379, 380), because electrical and metabolic activity rhythms within the SCN are similar (66, 91–94), as well as clock gene expression rhythms (109, 111, 114). Major differences in SCN efferent projections between nocturnal and diurnal mammals, including humans (381), have not been identified (382–384). This indicates that SCN outputs in diurnal and nocturnal mammals may be functionally different rather than structurally (382). In this section, we will highlight a downstream brain region that is possibly involved in diurnality, and discuss how several hormonal rhythms are differently regulated by the biological clock of diurnal and nocturnal species.

In both nocturnal and diurnal species, the most substantial part of SCN outputs projects to the subparaventricular zone (SPVZ). This structure borders the SCN (385, 386), and connects to areas the SCN also directly projects to (382, 386, 387). SPVZ involvement in circadian rhythms is shown through SPVZ lesions studies, in which disruption of activity

and sleep rhythms occurred (360, 388). Theoretically, the SPVZ has a perfect location to modulate SCN outputs and to function as a diurnality switch (17, 66). The electrical activity in the SPVZ has circadian rhythmicity and is 180° out of phase relative to the SCN in nocturnal rats (89, 389). In diurnal chipmunks however, neurons in the areas surrounding the SCN were active at the same time as the SCN (66). In accordance, Fos expression in the SPVZ was timed differently in diurnal Nile grass rats compared to nocturnal rats (296, 380, 390–392), indicating that differences in SPVZ activity may contribute to diurnality.

Three examples of hormonal rhythms controlled by the SCN, are the rhythms in glucocorticoid, melatonin and GnRH release (265, 301, 361, 362, 393, 394). Circadian glucocorticoid rhythms are regulated through rhythmic AVP release by projections from the SCN to the paraventricular nucleus and the dorsomedial hypothalamic nucleus (363, 395–397). Nocturnal rodents have a glucocorticoid peak at the end of the light period, while glucocorticoid rhythms in the diurnal species peak at the end of the dark period (27–30, 375). Kalsbeek *et al.* found that reversal of this glucocorticoid rhythm in diurnal grass rats could be accomplished by AVP projecting to glutamatergic rather than GABAergic neurons in the SPVZ (375). This mechanism allows AVP to exert an inhibitory effect on glucocorticoid release in nocturnal rodents, while stimulatory in diurnal rodents.

Melatonin release from the pineal gland is suppressed by light exposure (398) and shows a circadian rhythm with melatonin release during the night (21, 31–33). The SCN integrates photic input and regulates melatonin release via a direct multisynaptic neuronal pathway from the SCN to the pineal gland (399–402), consisting of inhibitory GABAergic signals (366, 403). For active melatonin stimulation, SCN neuronal activity during night time is required, despite the overall SCN electrical activity being low during the night (361, 401, 404). This is most likely mediated by a small glutamatergic SCN neuronal subpopulation, that was found to be active during night time (301, 362). The circadian melatonin rhythm peaks during night time for both diurnal and nocturnal mammals (21, 31–33), suggesting that diurnal and nocturnal species should respond differently to melatonin to have a rhythm enhancing effect. Indeed, in diurnal primates and humans, melatonin has a sleep promoting effect (405–408), whereas in nocturnal species melatonin does not affect sleep or even promotes waking (409, 410). Nonetheless, despite influencing sleep in diurnal primates and humans, no effect of melatonin was recognized on the circadian rhythm in diurnal Nile grass rats (411), degus (412) and ground squirrel (413).

Additionally, SCN projections to the preoptic area control the female menstrual cycle (393, 394, 414). In diurnal Nile grass rats, circadian Fos expression rhythms in gonadotropin-releasing hormone (GnRH) neurons are oppositely phased relative to nocturnal rodents, resulting in a differently timed postpartum luteinizing hormone surge (415, 416). Also the circadian timing of mating behaviour is reversed in diurnal grass rats (23, 417). Both the SCN itself and the SPVZ project to the GnRH neurons in diurnal grass rats, therefore it is

hypothesized that the output signal might be modulated by the SPVZ projections to establish a diurnal rhythm (382).

The SCN has more outputs than the three mentioned above, such as to the medial preoptic area, which is involved in thermoregulation (418, 419), and to the ventrolateral preoptic area and lateral hypothalamus, which are both involved in sleep-wake regulation (120, 420–422). It will require further research to identify all mechanisms enabling diurnality in various circadian output systems.

Taken together, these findings emphasize the heterogeneity of the mechanisms by which the various SCN outputs differ between diurnal and nocturnal species. For some hormonal rhythms (e.g. glucocorticoids and GnRH) the SPVZ appears to function as a diurnality switch (375, 415, 416), whereas other hormones (e.g. melatonin) affect sleep-wake timing differently to allow adaptation to a temporal niche (409). Although the SPVZ appears to be involved, a single diurnality switch that reverses all rhythms cannot be appointed. Research on the many different outputs of the SCN, both diffusible factors and electrical output, is required to chart the mechanisms contributing to diurnality.

7. Feedback to the SCN

The fourth functional component of the circadian system is feedback from peripheral oscillators and rhythms to the SCN (423). The target brain regions of the SCN output often have reciprocal connections with the SCN. In this chapter, we consider these brain areas to be feedback regions for the biological clock, because they influence the SCN rhythm, while being under circadian control themselves (424). For example, locomotor activity and sleep, both obviously influenced by the biological clock, appear to influence SCN electrical activity, thus providing feedback into the circadian system (425, 426). The first indications that behavioural activity feeds back into the SCN, were the observations that free-running periods of rats and mice with and without a running wheel differed (427–430) and that behavioural activity could even induce phase-shifts in hamsters (431, 432). Both diurnal and nocturnal species are in general sensitive to non-photic phase shifting during the subjective day (57, 425, 433). More evidence on behavioural feedback into the SCN, as mentioned earlier, are the observations that running wheel access may influence temporal niche preference in diurnal grass rats and degus (52, 81).

On the electrophysiological level, voluntary behavioural activity was found to suppress SCN electrical activity in nocturnal rats, hamsters and mice (92, 434, 435). Oppositely, in diurnal Sudanian grass rats, behavioural activity induced excitation in the SCN multi-unit activity (436). In both nocturnal and diurnal animals, this behavioural feedback will result in an increased SCN electrical activity amplitude: nocturnal species active during the night have more suppression in the trough of the SCN rhythm and diurnal species active during the day have more excitation at the peak (225, 435, 436). Photoperiod does not appear to be intrinsically encoded by SCN electrical activity in diurnal Sudanian grass rats *in vitro*

(357), opposite to observations in nocturnal species (12, 226–228, 304). Consequently, one might hypothesize that behavioural feedback may contribute more to circadian rhythms in diurnal compared to nocturnal species as a compensatory mechanism (357).

Some brain regions involved in behavioural feedback to the SCN are the IGL and the raphe nucleus. IGL neurons receive direct retinal input in diurnal (160) and nocturnal species (127, 437, 438), and they regulate the effect of photic (439, 440) and non-photic inputs into the circadian clock (441–444). The raphe nucleus feeds information about the alertness and vigilance back into the SCN (445, 446). These regions utilize neurotransmitters and neuropeptides, such as neuropeptide Y (NPY), GABA and serotonin, for providing feedback to the SCN (447–450). Likewise, melatonin from the pineal gland appears to have a feedback function to the circadian system (451, 452).

The IGL contains NPY neurons, projecting to the SCN core via the GHT (147, 447, 448, 453), which become activated upon wheel running in both diurnal and nocturnal species (453, 454). Electrical stimulation of the GHT (455) and NPY injection into the SCN can induce phase shifts (456, 457), while blocking NPY reduces behaviour-induced phase shifts, suggesting involvement of this tract in the integration of behavioural states to the clock (441). NPY is found in the SCN of diurnal thirteen-lined ground squirrel (*Spermophilus tridecemlineatus*) at different times than in nocturnal rats (458). Similarly, differences in NPY neuron activity in the IGL was revealed upon intraspecies comparison between diurnally and nocturnally active Nile grass rats: in diurnal grass rats NPY feedback occurs during the day and in nocturnal individuals during the night (453).

Neurons originating from the IGL also contain the inhibitory neurotransmitter GABA to deliver feedback to the SCN (449, 459). Although the GABA PRC is not shifted in diurnal grass rats, Novak *et al.* observed an important difference in GABA response between diurnal and nocturnal species (460, 461). Upon activation of GABA_A receptors with muscimol during daytime, nocturnal hamsters show a phase advances (462), while the diurnal Nile grass rats are delayed in phase (460, 461). Nevertheless, during the night, the GABAergic responses are similar for diurnal grass rats compared to nocturnal hamsters (460, 461).

Serotonin, originating from the raphe nucleus, is another mediator of feedback to the SCN (463–469). Injections of serotonergic agonists into the SCN during the subjective day induce large phase shifts in the behavioural activity of nocturnal mice and hamsters (470–472). Contrarily, Cuesta *et al.* found that diurnal Sudanian grass rats had an opposite window of sensitivity to serotonin, namely during the night (473). Additionally, the circadian rhythm of serotonin content in the SCN peaks at the end of the day for diurnal grass rats (473), instead of at the end of the night for nocturnal species (474).

While melatonin is generally known as a hormonal output rhythm of the circadian system, it also feeds back into the SCN (451, 452, 475–477), which contains melatonin receptors in most mammals (478–482). In both diurnal and nocturnal mammals, exogenous melatonin

administration can entrain behavioural rhythms (53, 483–486) and phase shift circadian activity *in vitro* (487, 488) and *in vivo* (489–491), with similar PRCs for diurnal grass rats (316) and nocturnal rats (492). In addition to its phase shifting effect, melatonin is found to suppress spontaneous SCN electrical activity (493, 494). Because this night time secretion coincides with already low SCN activity at night, melatonin presumably has a SCN amplitude increasing effect. However, the sensitivity window for exogenous melatonin does not overlap with the endogenous melatonin production, therefore melatonin feedback may be irrelevant for a normally functioning SCN (452, 495).

Generally, the effects of non-photoc stimuli on SCN rhythms are opposite to those of photic stimuli (109, 496–498). Non-photoc inputs are found to interact with light exposure (499–501), as for example shown by the ability of NPY to block glutamate or light-induced phase shifts, and vice versa, NPY-induced phase shifts being blocked by those (502, 503). The interaction of serotonin with light differs for diurnal and nocturnal species. While activation of serotonin signalling in the SCN attenuates light-induced phase shifts and SCN neuronal firing rates in nocturnal rodents (504–510), this interaction is reversed in diurnal grass rats, in which serotonin potentiates light-induced phase shifts (473). Nonetheless, more research should be conducted to exclude over-interpretation of interspecies differences, since variation in serotonin response also exists between nocturnal species (511). The interaction of GABA with light pulses is similar for diurnal and nocturnal species: GABA inhibits light-induced phase shifts during the subjective night in both (459–461).

The molecular mechanism underlying interactions of light and non-photoc stimuli involve PER gene regulation. In nocturnal species, light exposure increases PER expression in the SCN (111, 512–517), while NPY (518–520), serotonin (471) or GABA agonist injection (521) decrease PER expression. This explains why the non-photoc and photic PRC are generally oppositely phased: light can increase PER most effectively when it is already low during the night and non-photoc stimuli can decrease it when it is already high during the day (109). In contrast to other non-photoc stimuli, melatonin does not influence PER gene expression (522). While GABA agonist injection similarly decreases PER gene expression in diurnal Nile grass rats (115), it remains to be determined whether the other mechanisms of non-photoc feedback are altered in diurnal species.

In summary, accumulating evidence suggests that feedback mechanisms into the SCN differ between diurnal and nocturnal mammals. Importantly, SCN electrical activity is dissimilarly affected by behavioural activity in diurnal species (436), which is presumably caused by different sensitivity windows for involved neurotransmitters and neuropeptides (453, 461, 473). However, it is clear that feedback mechanisms influence the biological clock, and may have facilitated the evolutionary switch from nocturnality to diurnality in mammals.

8. Conclusion

For the last decades, the general hypothesis on diurnality has been that the major differences between diurnal and nocturnal species are located downstream of the SCN (17, 91, 379, 380, 523), due to similarities found in SCN electrical, metabolic and clock gene expression rhythms (66, 91, 93, 109, 111, 114). In this chapter, we suggested that diurnality is more complex than previously assumed. While differences downstream of the SCN are certainly present, fundamental differences in all functional components, including the SCN network itself, may contribute to diurnality (Table 2).

We surmise that there is no single diurnality switch, functioning as a simple sign switch. Rather, a variety of mechanisms, operating upstream, within and downstream from the SCN, may work together to establish the diurnal phenotype (17, 40, 41, 70, 85, 524). Such mechanisms may include the SCN network light response, downstream interpretation of the clock signals and response to non-photic feedback factors (85). Starting from a nocturnal ancestor, characteristics that stimulate nocturnal behaviour should decrease in power to allow the evolution of diurnal species. Enough of these characteristics should be dampened or reversed in order to allow full diurnality (17, 40, 41, 70, 85).

This theory would also explain why diurnal mammals are considerably more heterogeneous in their rhythm robustness and temporal niche preference than nocturnal mammals (17, 41, 47, 52, 62, 63, 85, 332, 334, 335) and why Aschoff's rule applies almost perfectly to all nocturnal but not to all diurnal species (4, 48, 51, 54, 62, 71, 331). The influence of multiple diurnality promoting traits on temporal niche explains why diurnality is best described as a continuous scale rather than a dichotomous characteristic (47). Species in the middle of the diurnality scale might have lost only some nocturnality promoting traits or acquired only some diurnality promoting traits (e.g. diurnal humans having a nocturnal-like retina) (177).

As a result, the intrinsic circadian activity rhythm of diurnal species might be less robust than in nocturnal species (47), and may therefore be more dependent on the many cycling variables in their environment (e.g. light, temperature, predators and food availability) (70). These factors differ between the natural habitat and research centres, which is the reason that temporal niche switching can occur upon transferring animals to the laboratory (39, 79, 525). The artificial fluctuations in ambient light in the laboratory might not be sufficient to stimulate natural behaviour. To make diurnality research more accurate, experimental conditions should match the natural conditions as much as possible, or even field observations should be performed. Furthermore, one should be very careful with breeding a fully diurnal animal model, in order to avoid selecting for characteristics that do not contribute to diurnality in the natural situation. It would be more informative to observe which mechanisms naturally evolved to promote diurnality. Importantly, mammalian diurnality evolved in multiple evolution lines independently (40), and could therefore be caused by different mechanisms (41, 334). These will not be

identified if researchers continue searching for a universal diurnality switch. Thus, in order to understand which mechanisms promote diurnality and which interspecies differences between nocturnal and diurnal species are meaningless for diurnality, it is essential to study and compare multiple diurnal species with multiple nocturnal species (194), while taking their position on the diurnality scale into account (47).

In conclusion, the many differences between diurnal and nocturnal mammals mentioned in this chapter certainly deserve additional investigation to evaluate their role as diurnality promoting factors. Although the significance of the neuronal organization within and surrounding the SCN network remains to be elucidated, diurnality definitely proves to be a more complex trait than previously assumed.

Table 2: Comparison of the circadian system in diurnal and nocturnal mammals

	Factor	Similarity	Reference
Organism	Locomotor activity	✗	By definition
	Body temperature	✗	Refinetti <i>et al.</i> 1996 (22)
	Glucocorticoid rhythm	✗	Halberg <i>et al.</i> 1959 (28)
	Melatonin rhythm	=	Reiter <i>et al.</i> 1985 (31)
Whole SCN	Metabolic activity rhythm	=	Schwartz <i>et al.</i> 1983 (93)
	Electrical activity rhythm	=	Sato & Kawamura 1984 (66)
Clock genes	Clock gene expression	=	Caldelas <i>et al.</i> 2003 (111)
Input	Light input pathway anatomy	=	Langel <i>et al.</i> 2015 (145)
	Cone percentage	✗	Hut <i>et al.</i> 2012 (39)
	Percentage light suppressed neurons	✗	Jiao <i>et al.</i> 1999 (206)
SCN network	Neuropeptide localization	=	Cohen <i>et al.</i> 2010 (271)
	VIP and GRP phase in constant darkness	✗	Dardente <i>et al.</i> 2004 (274)
	VIP and AVP phase relation	✗	Mammen <i>et al.</i> 2011 (159)
	Fos and neuropeptide colocalization	✗	Katona <i>et al.</i> 1998 (285)
	Light phase response curve	=	Lee & Labyak 1997 (48)
	Dead zone in phase response curve	✗	Beersma <i>et al.</i> 1999 (321)
	Dark pulse phase response curve	✗	Mendoza <i>et al.</i> 2007 (325)
	Period length and activity phase in constant light	✗	Aschoff <i>et al.</i> 1960 (4)
	Constant light intensities inducing splitting	✗	Meijer <i>et al.</i> 1990 (60)
	Rhythm robustness in constant conditions	✗	Refinetti <i>et al.</i> 2006 (332)
Output	SCN projections anatomy	=	Schwartz <i>et al.</i> 2011 (382)
	Fos expression in SPVZ	✗	Nunez <i>et al.</i> 1999 (390)

	AVP target neurons in glucocorticoid regulation	✗	Kalsbeek <i>et al.</i> 2008 (375)
	Effect of melatonin on sleep	✗	Huber <i>et al.</i> 1998 (409)
Feedback	Effect of behavioural activity on SCN electrical activity	✗	Schoonderwoerd <i>in preparation</i> (436)
	IGL activation upon wheel running	=	Smale <i>et al.</i> 2001 (453)
	GABA feedback PRC	✗	Novak <i>et al.</i> 2004 (461)
	Serotonin feedback PRC	✗	Cuesta <i>et al.</i> 2008 (473)
	Interaction of serotonin with light	✗	Cuesta <i>et al.</i> 2008 (473)
	Melatonin feedback PRC	=	Slotten <i>et al.</i> 2005 (316)

9. Outline of this thesis

The current thesis aims to elucidate the role of two input pathways to the circadian clock in nocturnality and diurnality: (i) light input and (ii) behavioural input. The first part focuses on how light information is processed in the nocturnal and the diurnal circadian system.

We discussed how diurnal species have higher percentages of cone photoreceptors compared to nocturnal species. To assess the impact of this difference, we test whether cones provide functional input to the circadian clock in **Chapter 2**. To this purpose, we examine whether transgenic mice that have only cones as functional photoreceptors (*Opn4^{-/-}Gnat1^{-/-}*) could entrain to light-dark cycles, phase shift activity rhythms after a light stimulus and show neuronal responses to light in the SCN. In **Chapter 3**, we investigate another factor that influences light sensitivity of the circadian system: sleep deprivation. Using electroretinography we examine the light responsiveness of the retina after sleep deprivation to determine whether the reduced light sensitivity originates at a retinal level or downstream.

In order to translate findings from nocturnal laboratory rodents to diurnal humans, we record responses of the human SCN to light in **Chapter 4**. Using a 7 Tesla MRI scanner, we perform functional SCN measurements in participants that are exposed to different colours of light. The light responses of the SCN neurons at the cellular level are investigated in **Chapter 5**. In this chapter, we prepare brain slices of the diurnal rodent *Rhabdomys pumilio* and nocturnal mice. We stimulate the retinohypothalamic tract electrically, to simulate light input, and compare the calcium responses in SCN neurons between the two species.

To determine whether the SCN of diurnal species responds differently to behavioural input, we record SCN activity in freely moving diurnal rodents *Arvicanthis ansorgei* in **Chapter 6**. Furthermore, we investigate how crepuscular behaviour (activity around dawn and dusk) affects SCN activity. In **Chapter 7**, we identify a phenomenon that likely reflects

the linkage of SCN activity and behaviour: the burst of locomotion at the unshifted phase (BLUP).

Finally, in **Chapter 8**, we discuss the findings of all studies performed and address the main question of this thesis: what is the role of the input pathways to the circadian clock in the regulation of nocturnality and diurnality?

References

1. S. M. Reppert, D. R. Weaver, Coordination of circadian timing in mammals. *Nature* **418**, 935–941 (2002).
2. C. S. Pittendrigh, Temporal organization: reflections of a Darwinian clock-watcher. *Annu Rev Physiol* **55**, 16–54 (1993).
3. D. R. Weaver, The suprachiasmatic nucleus: a 25-year retrospective. *J Biol Rhythms* **13**, 100–112 (1998).
4. J. ASCHOFF, Exogenous and endogenous components in circadian rhythms. *Cold Spring Harb Symp Quant Biol* **25**, 11–28 (1960).
5. R. Y. Moore, Organization and function of a central nervous system circadian oscillator: the suprachiasmatic hypothalamic nucleus. *Federation Proceedings* **42**, 2783–2789 (1983).
6. C. S. Pittendrigh, S. Daan, A functional analysis of circadian pacemakers in nocturnal rodents - I. The stability and lability of spontaneous frequency. *Journal of Comparative Physiology ??? A* **106**, 223–252 (1976).
7. S. Daan, C. S. Pittendrigh, A Functional analysis of circadian pacemakers in nocturnal rodents - II. The variability of phase response curves. *Journal of Comparative Physiology ??? A* **106**, 253–266 (1976).
8. B. Rusak, I. Zucker, Neural regulation of circadian rhythms. *Physiol Rev* **59**, 449–526 (1979).
9. C. S. PITTENDRIGH, Circadian rhythms and the circadian organization of living systems. *Cold Spring Harb Symp Quant Biol* **25**, 159–84 (1960).
10. J. Aschoff, Comparative Physiology: Diurnal Rhythms. *Annual Review of Physiology* **25**, 581–600 (1963).
11. C. S. Pittendrigh, S. Daan, A functional analysis of circadian pacemakers in nocturnal rodents - V. Pacemaker structure: A clock for all seasons. *Journal of Comparative Physiology ??? A* **106**, 333–355 (1976).
12. H. T. VanderLeest, *et al.*, Seasonal encoding by the circadian pacemaker of the SCN. *Current Biology* **17**, 468–73 (2007).
13. M. A. Hofman, D. F. Swaab, Diurnal and seasonal rhythms of neuronal activity in the suprachiasmatic nucleus of humans. *J Biol Rhythms* **8**, 283–95 (1993).
14. R. Y. Moore, N. J. Lenn, A retinohypothalamic projection in the rat. *J Comp Neurol* **146**, 1–14 (1972).
15. C. A. Czeisler, The effect of light on the human circadian pacemaker. *Ciba Found Symp* **183**, 254–90; discussion 290-302 (1995).
16. C. S. Pittendrigh, S. Daan, A functional analysis of circadian pacemakers in nocturnal rodents - IV. Entrainment: Pacemaker as clock. *Journal of Comparative Physiology ??? A* **106**, 291–331 (1976).

17. L. Smale, T. Lee, A. A. Nunez, Mammalian diurnality: some facts and gaps. *J Biol Rhythms* **18**, 356–66 (2003).
18. D. J. Dijk, C. A. Czeisler, Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* **15**, 3526–38 (1995).
19. S. Daan, D. G. Beersma, A. A. Borbély, Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol* **246**, R161-83 (1984).
20. C. A. Czeisler, E. d Weitzman, M. C. Moore-Ede, J. C. Zimmerman, R. S. Knauer, Human sleep: its duration and organization depend on its circadian phase. *Science* **210**, 1264–7 (1980).
21. E. Challet, Minireview: Entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. *Endocrinology* **148**, 5648–55 (2007).
22. R. Refinetti, Comparison of the body temperature rhythms of diurnal and nocturnal rodents. *J Exp Zool* **275**, 67–70 (1996).
23. T. L. McElhinny, L. Smale, K. E. Holekamp, Patterns of body temperature, activity, and reproductive behavior in a tropical murid rodent, *Arvicanthis niloticus*. *Physiol Behav* **62**, 91–6 (1997).
24. R. Refinetti, Relationship between the daily rhythms of locomotor activity and body temperature in eight mammalian species. *Am J Physiol* **277**, R1493-500 (1999).
25. C. Benstaali, A. Mailloux, A. Bogdan, A. Auzéby, Y. Touitou, Circadian rhythms of body temperature and motor activity in rodents their relationships with the light-dark cycle. *Life Sci* **68**, 2645–56 (2001).
26. H. C. MELLETTE, B. K. HUTT, S. I. ASKOVITZ, S. M. HORVATH, Diurnal variations in body temperatures. *J Appl Physiol* **3**, 665–75 (1951).
27. D. N. Orth, D. P. Island, Light synchronization of the circadian rhythm in plasma cortisol (17-OHCS) concentration in man. *J Clin Endocrinol Metab* **29**, 479–86 (1969).
28. F. HALBERG, R. E. PETERSON, R. H. SILBER, Phase relations of 24-hour periodicities in blood corticosterone, mitoses in cortical adrenal parenchyma, and total body activity. *Endocrinology* **64**, 222–30 (1959).
29. L. A. W. Verhagen, *et al.*, Temporal organization of the 24-h corticosterone rhythm in the diurnal murid rodent *Arvicanthis ansorgei* Thomas 1910. *Brain Res* **995**, 197–204 (2004).
30. A. Kalsbeek, *et al.*, Circadian rhythms in the hypothalamo-pituitary-adrenal (HPA) axis. *Mol Cell Endocrinol* **349**, 20–9 (2012).
31. R. J. Reiter, Action spectra, dose-response relationships, and temporal aspects of light's effects on the pineal gland. *Ann N Y Acad Sci* **453**, 215–30 (1985).
32. M.-L. Garidou, *et al.*, Pineal arylalkylamine N-acetyltransferase gene expression is highly stimulated at night in the diurnal rodent, *Arvicanthis ansorgei*. *Eur J Neurosci* **15**, 1632–40 (2002).
33. D. Dawson, C. J. van den Heuvel, Integrating the actions of melatonin on human physiology. *Ann Med* **30**, 95–102 (1998).
34. A. W. Crompton, C. R. Taylor, J. A. Jagger, Evolution of homeothermy in mammals. *Nature* **272**, 333–6 (1978).

35. M. Menaker, L. F. Moreira, G. Tosini, Evolution of circadian organization in vertebrates. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas médicas e biológicas / Sociedade Brasileira de Biofísica ... [et al.]* **30**, 305–13 (1997).
36. C. P. Heesy, M. I. Hall, The nocturnal bottleneck and the evolution of mammalian vision. *Brain Behav Evol* **75**, 195–203 (2010).
37. M. P. Gerkema, W. I. L. Davies, R. G. Foster, M. Menaker, R. A. Hut, The nocturnal bottleneck and the evolution of activity patterns in mammals. *Proceedings. Biological sciences / The Royal Society* **280**, 20130508 (2013).
38. W. I. L. Davies, S. P. Collin, D. M. Hunt, Molecular ecology and adaptation of visual photopigments in craniates. *Mol Ecol* **21**, 3121–58 (2012).
39. R. A. Hut, N. Kronfeld-Schor, V. van der Vinne, H. De la Iglesia, In search of a temporal niche: environmental factors. *Prog Brain Res* **199**, 281–304 (2012).
40. U. Roll, T. Dayan, N. Kronfeld-Schor, On the role of phylogeny in determining activity patterns of rodents. *Evolutionary Ecology* **20**, 479–490 (2006).
41. L. Smale, A. a Nunez, M. D. Schwartz, Rhythms in a diurnal brain. *Biological Rhythm Research* **39**, 305–318 (2008).
42. K. Honma, F. Katabami, T. Hiroshige, A phase response curve for the locomotor activity rhythm of the rat. *Experientia* **34**, 1602–3 (1978).
43. K. Honma, S. Honma, T. Hiroshige, Response curve, free-running period, and activity time in circadian locomotor rhythm of rats. *Jpn J Physiol* **35**, 643–58 (1985).
44. M. Comas, D. G. M. Beersma, K. Spoelstra, S. Daan, Phase and period responses of the circadian system of mice (*Mus musculus*) to light stimuli of different duration. *J Biol Rhythms* **21**, 362–72 (2006).
45. J. Aschoff, Die 24-Stunden-Periodik der Maus unter konstanten Umgebungsbedingungen. *Naturwissenschaften* **38**, 506–507 (1951).
46. J. H. Meijer, B. Rusak, G. Gänshirt, The relation between light-induced discharge in the suprachiasmatic nucleus and phase shifts of hamster circadian rhythms. *Brain Research* **598**, 257–63 (1992).
47. R. Refinetti, Variability of diurnality in laboratory rodents. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* **192**, 701–14 (2006).
48. T. M. Lee, S. E. Labyak, Free-running rhythms and light- and dark-pulse phase response curves for diurnal *Octodon degus* (Rodentia). *Am J Physiol* **273**, R278-86 (1997).
49. R. García-Allegue, P. Lax, A. M. Madariaga, J. A. Madrid, Locomotor and feeding activity rhythms in a light-entrained diurnal rodent, *Octodon degus*. *Am J Physiol* **277**, R523-31 (1999).
50. G. W. Fulk, Notes on the Activity, Reproduction, and Social Behavior of *Octodon degus*. *Journal of Mammalogy* **57**, 495–505 (1976).
51. C. Katona, L. Smale, Wheel-running rhythms in *Arvicanthis niloticus*. *Physiol Behav* **61**, 365–72 (1997).
52. J. A. Blanchong, T. L. McElhinny, M. M. Mahoney, L. Smale, Nocturnal and diurnal rhythms in the unstriped Nile rat, *Arvicanthis niloticus*. *J Biol Rhythms* **14**, 364–77 (1999).

53. H. A. Sloten, S. Krekling, B. Sicard, P. Pévet, Daily infusion of melatonin entrains circadian activity rhythms in the diurnal rodent *Arvicanthis ansorgei*. *Behavioural brain research* **133**, 11–9 (2002).
54. E. Challet, B. Pitrosky, B. Sicard, A. Malan, P. Pévet, Circadian organization in a diurnal rodent, *Arvicanthis ansorgei* Thomas 1910: chronotypes, responses to constant lighting conditions, and photoperiodic changes. *J Biol Rhythms* **17**, 52–64 (2002).
55. M. Cuesta, D. Clesse, P. Pévet, E. Challet, From daily behavior to hormonal and neurotransmitters rhythms: comparison between diurnal and nocturnal rat species. *Horm Behav* **55**, 338–47 (2009).
56. R. A. Hut, B. E. van Oort, S. Daan, Natural entrainment without dawn and dusk: the case of the European ground squirrel (*Spermophilus citellus*). *J Biol Rhythms* **14**, 290–9 (1999).
57. R. A. Hut, N. Mrosovsky, S. Daan, Nonphotic entrainment in a diurnal mammal, the European ground squirrel (*Spermophilus citellus*). *J Biol Rhythms* **14**, 409–19 (1999).
58. K. Hoffmann, Circadiane Periodik bei Tupaia (*Tupaia glis*) in konstanten Bedingungen. *Zool. Anz.* **33**, 171–177 (1969).
59. K. Hoffmann, “Splitting of the circadian rhythm as a function of light intensity” in *Biochronometry*, M. Menaker, Ed. (National Academy Press, 1971), pp. 134–150.
60. J. H. Meijer, S. Daan, G. J. Overkamp, P. M. Hermann, The two-oscillator circadian system of tree shrews (*Tupaia belangeri*) and its response to light and dark pulses. *J Biol Rhythms* **5**, 1–16 (1990).
61. R. Refinetti, The diversity of temporal niches in mammals. *Biological Rhythm Research* **39**, 173–192 (2008).
62. R. Cohen, N. Kronfeld-Schor, Individual variability and photic entrainment of circadian rhythms in golden spiny mice. *Physiol Behav* **87**, 563–74 (2006).
63. R. Cohen, L. Smale, N. Kronfeld-Schor, Plasticity of circadian activity and body temperature rhythms in golden spiny mice. *Chronobiol Int* **26**, 430–46 (2009).
64. H. Pohl, Light pulses entrain the circadian activity rhythm of a diurnal rodent (*Ammospermophilus leucurus*). *Comp Biochem Physiol B* **76**, 723–9 (1983).
65. D. E. F. L. Flôres, B. M. Tomotani, P. Tachinardi, G. A. Oda, V. S. Valentinuzzi, Modeling natural photic entrainment in a subterranean rodent (*Ctenomys aff. knighti*), the Tuco-Tuco. *PLoS One* **8**, e68243 (2013).
66. T. Sato, H. Kawamura, Circadian rhythms in multiple unit activity inside and outside the suprachiasmatic nucleus in the diurnal chipmunk (*Eutamias sibiricus*). *Neurosci Res* **1**, 45–52 (1984).
67. K. Navaneethakannan, M. K. Chandrashekar, Light and dark pulse response curves in a day active palm squirrel *Funambulus palmarum*. *Exp Biol* **45**, 267–73 (1986).
68. M. Lahmam, *et al.*, Daily behavioral rhythmicity and organization of the suprachiasmatic nuclei in the diurnal rodent, *Lemniscomys barbarus*. *Chronobiol Int* **25**, 882–904 (2008).
69. D. Weinert, R. Weinandy, R. Gattermann, Photic and non-photic effects on the daily activity pattern of Mongolian gerbils. *Physiol Behav* **90**, 325–33 (2007).
70. O. Barak, N. Kronfeld-Schor, Activity rhythms and masking response in the diurnal fat sand rat under laboratory conditions. *Chronobiol Int* **30**, 1123–34 (2013).

71. D. M. Schumann, H. M. Cooper, M. D. Hofmeyr, N. C. Bennett, Circadian rhythm of locomotor activity in the four-striped field mouse, *Rhabdomys pumilio*: a diurnal African rodent. *Physiol Behav* **85**, 231–9 (2005).
72. J. H. Meijer, B. Rusak, M. E. Harrington, Photically responsive neurons in the hypothalamus of a diurnal ground squirrel. *Brain Research* **501**, 315–323 (1989).
73. K. R. Kramm, D. A. Kramm, Photoperiodic control of circadian activity rhythms in diurnal rodents. *Int J Biometeorol* **24**, 65–76 (1980).
74. N. Zisapel, E. Barnea, I. Izhaki, Y. Anis, A. Haim, Daily scheduling of the golden spiny mouse under photoperiodic and social cues. *J Exp Zool* **284**, 100–6 (1999).
75. I. Caldelas, *et al.*, Timed hypocaloric feeding and melatonin synchronize the suprachiasmatic clockwork in rats, but with opposite timing of behavioral output. *Eur J Neurosci* **22**, 921–9 (2005).
76. V. van der Vinne, *et al.*, Cold and hunger induce diurnality in a nocturnal mammal. *Proc Natl Acad Sci U S A* **111**, 15256–60 (2014).
77. A. Castillo-Ruiz, M. J. Paul, W. J. Schwartz, In search of a temporal niche: social interactions. *Prog Brain Res* **199**, 267–80 (2012).
78. N. Kronfeld-Schor, T. Dayan, Partitioning of Time as an Ecological Resource. *Annual Review of Ecology, Evolution, and Systematics* **34**, 153–181 (2003).
79. O. Levy, T. Dayan, N. Kronfeld-Schor, The relationship between the golden spiny mouse circadian system and its diurnal activity: an experimental field enclosures and laboratory study. *Chronobiol Int* **24**, 599–613 (2007).
80. P. Tachinardi, Ø. Tøien, V. S. Valentinuzzi, C. L. Buck, G. A. Oda, Nocturnal to Diurnal Switches with Spontaneous Suppression of Wheel-Running Behavior in a Subterranean Rodent. *PLoS One* **10**, e0140500 (2015).
81. M. J. Kas, D. M. Edgar, A nonphotic stimulus inverts the diurnal-nocturnal phase preference in *Octodon degus*. *J Neurosci* **19**, 328–33 (1999).
82. A. Ocampo-Garcés, F. Hernández, W. Mena, A. G. Palacios, Wheel-running and rest activity pattern interaction in two octodontids (*Octodon degus*, *Octodon bridgesi*). *Biological Research* **38**, 299–305 (2005).
83. V. van der Vinne, J. A. Gorter, S. J. Riede, R. A. Hut, Diurnality as an energy-saving strategy: energetic consequences of temporal niche switching in small mammals. *J Exp Biol* **218**, 2585–93 (2015).
84. R. A. Hut, V. Pilorz, A. S. Boerema, A. M. Strijkstra, S. Daan, Working for food shifts nocturnal mouse activity into the day. *PLoS One* **6**, e17527 (2011).
85. N. Kronfeld-Schor, T. Dayan, Activity patterns of rodents: the physiological ecology of biological rhythms. *Biological Rhythm Research* **39**, 193–211 (2008).
86. R. Y. Moore, V. B. Eichler, Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Research* **42**, 201–206 (1972).
87. F. K. Stephan, I. Zucker, Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc Natl Acad Sci U S A* **69**, 1583–1586 (1972).

88. I. Zucker, M. Boshes, J. Dark, Suprachiasmatic nuclei influence circannual and circadian rhythms of ground squirrels. *Am J Physiol* **244**, R472-80 (1983).
89. S. T. Inouye, H. Kawamura, Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. *Proc Natl Acad Sci U S A* **76**, 5962–5966 (1979).
90. S. Shibata, Y. Oomura, H. Kita, K. Hattori, Circadian rhythmic changes of neuronal activity in the suprachiasmatic nucleus of the rat hypothalamic slice. *Brain Research* **247**, 154–158 (1982).
91. S. Kurumiya, H. Kawamura, Circadian oscillation of the multiple unit activity in the guinea pig suprachiasmatic nucleus. *J Comp Physiol A* **162**, 301–8 (1988).
92. S. Yamazaki, M. C. Kerbeshian, C. G. Hocker, G. D. Block, M. Menaker, Rhythmic properties of the hamster suprachiasmatic nucleus in vivo. *J Neurosci* **18**, 10709–23 (1998).
93. W. J. Schwartz, S. M. Reppert, S. M. Egan, M. C. Moore-Ede, In vivo metabolic activity of the suprachiasmatic nuclei: a comparative study. *Brain Res* **274**, 184–7 (1983).
94. W. J. Schwartz, L. C. Davidsen, C. B. Smith, In vivo metabolic activity of a putative circadian oscillator, the rat suprachiasmatic nucleus. *J Comp Neurol* **189**, 157–67 (1980).
95. D. K. Welsh, D. E. Logothetis, M. Meister, S. M. Reppert, Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron* **14**, 697–706 (1995).
96. A. B. Webb, N. Angelo, J. E. Huettnner, E. D. Herzog, Intrinsic, nondeterministic circadian rhythm generation in identified mammalian neurons. *Proc Natl Acad Sci U S A* **106**, 16493–8 (2009).
97. E. D. Herzog, J. S. Takahashi, G. D. Block, Clock controls circadian period in isolated suprachiasmatic nucleus neurons. *Nat Neurosci* **1**, 708–713 (1998).
98. S. Honma, T. Shirakawa, Y. Katsuno, M. Namihira, K. Honma, Circadian periods of single suprachiasmatic neurons in rats. *Neurosci Lett* **250**, 157–60 (1998).
99. W. J. Schwartz, H. Gainer, Suprachiasmatic nucleus: use of ¹⁴C-labeled deoxyglucose uptake as a functional marker. *Science* **197**, 1089–1091 (1977).
100. C. Liu, D. R. Weaver, S. H. Strogatz, S. M. Reppert, Cellular construction of a circadian clock: period determination in the suprachiasmatic nuclei. *Cell* **91**, 855–60 (1997).
101. D. J. Green, R. Gillette, Circadian rhythm of firing rate recorded from single cells in the rat suprachiasmatic brain slice. *Brain Research* **245**, 198–200 (1982).
102. G. Groos, J. Hendriks, Circadian rhythms in electrical discharge of rat suprachiasmatic neurones recorded in vitro. *Neuroscience Letters* **34**, 283–288 (1982).
103. S. M. Reppert, D. R. Weaver, Molecular Analysis of Mammalian Circadian Rhythms. *Annual Review of Physiology* **63**, 647–676 (2001).
104. J. C. Dunlap, Molecular bases for circadian clocks. *Cell* **96**, 271–90 (1999).
105. L. P. Shearman, *et al.*, Interacting molecular loops in the mammalian circadian clock. *Science* **288**, 1013–9 (2000).
106. D. P. King, J. S. Takahashi, Molecular genetics of circadian rhythms in mammals. *Annual Review of Neuroscience* **23**, 713–742 (2000).

107. I. Chakir, *et al.*, The circadian gene Clock oscillates in the suprachiasmatic nuclei of the diurnal rodent Barbary striped grass mouse, *Lemniscomys barbarus*: a general feature of diurnality? *Brain Res* **1594**, 165–72 (2015).
108. A. M. Vosko, M. H. Hagenauer, D. L. Hummer, T. M. Lee, Period gene expression in the diurnal degu (*Octodon degus*) differs from the nocturnal laboratory rat (*Rattus norvegicus*). *Am J Physiol Regul Integr Comp Physiol* **296**, R353–61 (2009).
109. N. Mrosovsky, K. Edelman, M. H. Hastings, E. S. Maywood, Cycle of period gene expression in a diurnal mammal (*Spermophilus tridecemlineatus*): implications for nonphotic phase shifting. *J Biol Rhythms* **16**, 471–8 (2001).
110. G. Lincoln, S. Messenger, H. Andersson, D. Hazlerigg, Temporal expression of seven clock genes in the suprachiasmatic nucleus and the pars tuberalis of the sheep: evidence for an internal coincidence timer. *Proc Natl Acad Sci U S A* **99**, 13890–5 (2002).
111. I. Caldelas, V. J. Poirel, B. Sicard, P. Pevet, E. Challet, Circadian profile and photic regulation of clock genes in the suprachiasmatic nucleus of a diurnal mammal *Arvicanthis ansorgei*. *Neuroscience* **116**, 583–591 (2003).
112. C. Ramanathan, A. A. Nunez, G. S. Martinez, M. D. Schwartz, L. Smale, Temporal and spatial distribution of immunoreactive PER1 and PER2 proteins in the suprachiasmatic nucleus and peri-suprachiasmatic region of the diurnal grass rat (*Arvicanthis niloticus*). *Brain Res* **1073–1074**, 348–58 (2006).
113. J. M. Koch, M. H. Hagenauer, T. M. Lee, The response of Per1 to light in the suprachiasmatic nucleus of the diurnal degu (*Octodon degus*). *Chronobiol Int* **26**, 1263–71 (2009).
114. C. Ramanathan, *et al.*, Compartmentalized expression of light-induced clock genes in the suprachiasmatic nucleus of the diurnal grass rat (*Arvicanthis niloticus*). *Neuroscience* **161**, 960–9 (2009).
115. C. M. Novak, J. C. Ehlen, K. N. Paul, C. Fukuhara, H. E. Albers, Light and GABA(A) receptor activation alter period mRNA levels in the SCN of diurnal Nile grass rats. *Eur J Neurosci* **24**, 2843–52 (2006).
116. J. Aschoff, Circadian Rhythms in Man. *Science (1979)* **148**, 1427–1432 (1965).
117. P. J. DECOURSEY, Phase control of activity in a rodent. *Cold Spring Harb Symp Quant Biol* **25**, 49–55 (1960).
118. G. E. Pickard, The afferent connections of the suprachiasmatic nucleus of the golden hamster with emphasis on the retinohypothalamic projection. *J Comp Neurol* **211**, 65–83 (1982).
119. R. F. Johnson, L. P. Morin, R. Y. Moore, Retinohypothalamic projections in the hamster and rat demonstrated using cholera toxin. *Brain Res* **462**, 301–12 (1988).
120. E. E. Abrahamson, R. Y. Moore, Suprachiasmatic nucleus in the mouse: retinal innervation, intrinsic organization and efferent projections. *Brain Res* **916**, 172–91 (2001).
121. M. S. Freedman, *et al.*, Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. *Science (1979)* **284**, 502–504 (1999).
122. J. S. Takahashi, P. J. DeCoursey, L. Bauman, M. Menaker, Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. *Nature* **308**, 186–8 (1984).
123. S. Panda, *et al.*, Melanopsin is required for non-image-forming photic responses in blind mice. *Science* **301**, 525–7 (2003).

124. C. a Czeisler, *et al.*, "Suppression of melatonin secretion in some blind patients by exposure to bright light." (1995).
125. R. Y. Moore, J. C. Speh, J. P. Card, The retinohypothalamic tract originates from a distinct subset of retinal ganglion cells. *Journal of Comparative Neurology* **352**, 351–366 (1995).
126. D. M. Berson, F. A. Dunn, M. Takao, Phototransduction by retinal ganglion cells that set the circadian clock. *Science* **295**, 1070–1073 (2002).
127. S. Hattar, *et al.*, Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J Comp Neurol* **497**, 326–49 (2006).
128. S. Hattar, H. W. Liao, M. Takao, D. M. Berson, K. W. Yau, Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* **295**, 1065–1070 (2002).
129. J. J. Gooley, J. Lu, T. C. Chou, T. E. Scammell, C. B. Saper, Melanopsin in cells of origin of the retinohypothalamic tract. *Nat Neurosci* **4**, 1165 (2001).
130. I. Provencio, *et al.*, A novel human opsin in the inner retina. *J Neurosci* **20**, 600–605 (2000).
131. G. C. Brainard, *et al.*, Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci* **21**, 6405–6412 (2001).
132. D. M. Dacey, *et al.*, Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature* **433**, 749–754 (2005).
133. A. D. Güler, *et al.*, Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. *Nature* **453**, 102–105 (2008).
134. M. A. Belenky, C. A. Smeraski, I. Provencio, P. J. Sollars, G. E. Pickard, Melanopsin retinal ganglion cells receive bipolar and amacrine cell synapses. *Journal of Comparative Neurology* **460**, 380–393 (2003).
135. N. C. Aggelopoulos, H. Meissl, Responses of neurones of the rat suprachiasmatic nucleus to retinal illumination under photopic and scotopic conditions. *J Physiol* **523 Pt 1**, 211–222 (2000).
136. J. A. Perez-Leon, E. J. Warren, C. N. Allen, D. W. Robinson, B. R. Lane, Synaptic inputs to retinal ganglion cells that set the circadian clock. *European Journal of Neuroscience* **24**, 1117–1123 (2006).
137. T. M. Schmidt, P. Kofuji, Differential cone pathway influence on intrinsically photosensitive retinal ganglion cell subtypes. *J Neurosci* **30**, 16262–71 (2010).
138. K. Y. Wong, F. A. Dunn, D. M. Graham, D. M. Berson, Synaptic influences on rat ganglion-cell photoreceptors. *J Physiol* **582**, 279–296 (2007).
139. S. Hattar, *et al.*, Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. *Nature* **424**, 76–81 (2003).
140. J. Østergaard, J. Hannibal, J. Fahrenkrug, Synaptic contact between melanopsin-containing retinal ganglion cells and rod bipolar cells. *Investigative Ophthalmology and Visual Science* **48**, 3812–3820 (2007).
141. G. WALD, P. K. BROWN, P. H. SMITH, Iodopsin. *J Gen Physiol* **38**, 623–81 (1955).
142. J. Dai, J. Van Der Vliet, D. F. Swaab, R. M. Buijs, Human retinohypothalamic tract as revealed by in vitro postmortem tracing. *Journal of Comparative Neurology* **397**, 357–370 (1998).

143. J. Hannibal, *et al.*, Melanopsin is expressed in PACAP-containing retinal ganglion cells of the human retinohypothalamic tract. *Invest Ophthalmol Vis Sci* **45**, 4202–9 (2004).
144. J. Hannibal, J. Fahrenkrug, Target areas innervated by PACAP-immunoreactive retinal ganglion cells. *Cell Tissue Res* **316**, 99–113 (2004).
145. J. L. Langel, L. Smale, G. Esquivia, J. Hannibal, Central melanopsin projections in the diurnal rodent, *Arvicanthis niloticus*. *Front Neuroanat* **9**, 93 (2015).
146. D. Karnas, D. Hicks, J. Mordel, P. Pévet, H. Meissl, Intrinsic photosensitive retinal ganglion cells in the diurnal rodent, *Arvicanthis ansorgei*. *PLoS One* **8**, e73343 (2013).
147. N. Goel, T. M. Lee, L. Smale, Suprachiasmatic nucleus and intergeniculate leaflet in the diurnal rodent *Octodon degus*: retinal projections and immunocytochemical characterization. *Neuroscience* **92**, 1491–509 (1999).
148. F. Gaillard, H. J. Karten, Y. Sauvé, Retinorecipient areas in the diurnal murine rodent *Arvicanthis niloticus*: a disproportionally large superior colliculus. *J Comp Neurol* **521**, 1699–726 (2013).
149. R. Y. Moore, Organization of the mammalian circadian system. *Ciba Found Symp* **183**, 88–99; discussion 100–6 (1995).
150. L. P. Morin, C. N. Allen, The circadian visual system, 2005. *Brain Res Rev* **51**, 1–60 (2006).
151. J. P. Card, R. Y. Moore, Ventral lateral geniculate nucleus efferents to the rat suprachiasmatic nucleus exhibit avian pancreatic polypeptide-like immunoreactivity. *J Comp Neurol* **206**, 390–6 (1982).
152. G. H. Jacobs, The distribution and nature of colour vision among the mammals. *Biol Rev Camb Philos Soc* **68**, 413–71 (1993).
153. T. H. Goldsmith, Optimization, constraint, and history in the evolution of eyes. *Q Rev Biol* **65**, 281–322 (1990).
154. C. P. van Schaik, M. Griffiths, Activity periods of Indonesian rain forest mammals. *Biotropica* **28**, 105–112 (1996).
155. E. C. Kirk, Comparative morphology of the eye in primates. *Anat Rec A Discov Mol Cell Evol Biol* **281**, 1095–103 (2004).
156. I. Solovei, *et al.*, Nuclear architecture of rod photoreceptor cells adapts to vision in mammalian evolution. *Cell* **137**, 356–68 (2009).
157. K. C. Wikler, P. Rakic, Distribution of photoreceptor subtypes in the retina of diurnal and nocturnal primates. *J Neurosci* **10**, 3390–401 (1990).
158. K. Linberg, N. Cuenca, P. Ahnelt, S. Fisher, H. Kolb, Comparative anatomy of major retinal pathways in the eyes of nocturnal and diurnal mammals. *Progress in Brain Research* **131**, 27–52 (2001).
159. A. P. Mammen, A. Jagota, Immunocytochemical evidence for different patterns in daily rhythms of VIP and AVP peptides in the suprachiasmatic nucleus of diurnal *Funambulus palmarum*. *Brain Res* **1373**, 39–47 (2011).
160. L. Smale, J. Boverhof, The suprachiasmatic nucleus and intergeniculate leaflet of *Arvicanthis niloticus*, a diurnal murid rodent from East Africa. *J Comp Neurol* **403**, 190–208 (1999).

161. H. Kita, Y. Oomura, An anterograde HRP study of retinal projections to the hypothalamus in the rat. *Brain Res Bull* **8**, 249–53 (1982).
162. R. A. Hut, A. Scheper, S. Daan, Can the circadian system of a diurnal and a nocturnal rodent entrain to ultraviolet light? *J Comp Physiol A* **186**, 707–15 (2000).
163. G. H. Jacobs, J. B. Calderone, J. A. Fenwick, K. Krogh, G. A. Williams, Visual adaptations in a diurnal rodent, *Octodon degus*. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* **189**, 347–61 (2003).
164. A. Ringvold, Aqueous humour and ultraviolet radiation. *Acta Ophthalmol* **58**, 69–82 (1980).
165. J. Nathan, *et al.*, Scotopic and photopic visual thresholds and spatial and temporal discrimination evaluated by behavior of mice in a water maze. *Photochem Photobiol* **82**, 1489–1494 (2006).
166. I. Perlman, R. a Normann, Light adaptation and sensitivity controlling mechanisms in vertebrate photoreceptors. *Prog Retin Eye Res* **17**, 523–63 (1998).
167. F. Ankel-Simons, D. T. Rasmussen, Diurnality, nocturnality, and the evolution of primate visual systems. *Am J Phys Anthropol Suppl* **47**, 100–17 (2008).
168. C. J. Jeon, E. Strettoi, R. H. Masland, The major cell populations of the mouse retina. *J Neurosci* **18**, 8936–46 (1998).
169. L. D. Carter-Dawson, M. M. LaVail, Rods and cones in the mouse retina. I. Structural analysis using light and electron microscopy. *J Comp Neurol* **188**, 245–62 (1979).
170. M. M. La Vail, Survival of some photoreceptor cells in albino rats following long-term exposure to continuous light. *Invest Ophthalmol* **15**, 64–70 (1976).
171. A. Szél, P. Röhlich, Two cone types of rat retina detected by anti-visual pigment antibodies. *Exp Eye Res* **55**, 47–52 (1992).
172. C. Bobu, C. M. Craft, M. Masson-Pevet, D. Hicks, Photoreceptor organization and rhythmic phagocytosis in the nile rat *Arvicanthis ansorgei*: a novel diurnal rodent model for the study of cone pathophysiology. *Invest Ophthalmol Vis Sci* **47**, 3109–18 (2006).
173. C. Bobu, M. Lahmam, P. Vuillez, A. Ouarour, D. Hicks, Photoreceptor organisation and phenotypic characterization in retinas of two diurnal rodent species: potential use as experimental animal models for human vision research. *Vision Res* **48**, 424–32 (2008).
174. F. Gaillard, *et al.*, Retinal anatomy and visual performance in a diurnal cone-rich laboratory rodent, the Nile grass rat (*Arvicanthis niloticus*). *J Comp Neurol* **510**, 525–38 (2008).
175. A. Szél, P. Röhlich, Four photoreceptor types in the ground squirrel retina as evidenced by immunocytochemistry. *Vision Res* **28**, 1297–302 (1988).
176. B. Müller, L. Peichl, Topography of cones and rods in the tree shrew retina. *J Comp Neurol* **282**, 581–94 (1989).
177. C. A. Curcio, K. R. Sloan, R. E. Kalina, A. E. Hendrickson, Human photoreceptor topography. *J Comp Neurol* **292**, 497–523 (1990).
178. D. L. Boudard, *et al.*, Cone loss is delayed relative to rod loss during induced retinal degeneration in the diurnal cone-rich rodent *Arvicanthis ansorgei*. *Neuroscience* **169**, 1815–30 (2010).

179. J. J. Gooley, *et al.*, Spectral responses of the human circadian system depend on the irradiance and duration of exposure to light. *Sci Transl Med* **2**, 31ra33 (2010).
180. J. J. Gooley, *et al.*, Melanopsin and Rod-Cone Photoreceptors Play Different Roles in Mediating Pupillary Light Responses during Exposure to Continuous Light in Humans. *Journal of Neuroscience* **32**, 14242–14253 (2012).
181. O. Dkhissi-Benyahya, C. Gronfier, W. De Vanssay, F. Flamant, H. M. Cooper, Modeling the Role of Mid-Wavelength Cones in Circadian Responses to Light. *Neuron* **53**, 677–687 (2007).
182. G. S. Lall, *et al.*, Distinct contributions of rod, cone, and melanopsin photoreceptors to encoding irradiance. *Neuron* **66**, 417–428 (2010).
183. T. M. Brown, J. Wynne, H. D. Piggins, R. J. Lucas, Multiple hypothalamic cell populations encoding distinct visual information. *J Physiol* **589**, 1173–1194 (2011).
184. A. Ramkisoensing, H. C. van Diepen, R. A. Schoonderwoerd, S. Hattar, J. H. Meijer, Cone photoreceptors contribute to the light response of the mammalian biological clock. *In preparation*.
185. L. Walmsley, *et al.*, Colour As a Signal for Entraining the Mammalian Circadian Clock. *PLOS Biology* **13**, e1002127 (2015).
186. H. C. Van Diepen, A. Ramkisoensing, S. N. Peirson, R. G. Foster, J. H. Meijer, Irradiance encoding in the suprachiasmatic nuclei by rod and cone photoreceptors. *FASEB Journal* **27**, 4204–4212 (2013).
187. H. C. van Diepen, R. G. Foster, J. H. Meijer, A colourful clock. *PLoS Biol* **13**, e1002160 (2015).
188. A. E. Allen, *et al.*, Melanopsin-driven light adaptation in mouse vision. *Curr Biol* **24**, 2481–90 (2014).
189. D. E. Nelson, J. S. Takahashi, Comparison of visual sensitivity for suppression of pineal melatonin and circadian phase-shifting in the golden hamster. *Brain Res* **554**, 272–7 (1991).
190. C. A. Czeisler, *et al.*, Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science* **244**, 1328–33 (1989).
191. D. B. Boivin, J. F. Duffy, R. E. Kronauer, C. A. Czeisler, Dose-response relationships for resetting of human circadian clock by light. *Nature* **379**, 540–2 (1996).
192. H. Pohl, “Characteristics and variability in entrainment of circadian rhythms to light in diurnal rodents” in *Vertebrate Circadian Systems*, J. Aschoff, S. Daan, G. A. Groos, Eds. (1982), pp. 339–346.
193. R. J. Reiter, S. Steinlechner, B. A. Richardson, T. S. King, Differential response of pineal melatonin levels to light at night in laboratory-raised and wild-captured 13-lined ground squirrels (*Spermophilus tridecemlineatus*). *Life Sci* **32**, 2625–9 (1983).
194. N. Mrosovsky, S. Hattar, Diurnal mice (*Mus musculus*) and other examples of temporal niche switching. *Journal of Comparative Physiology A: Neuroethology, Sensory, Neural, and Behavioral Physiology* **191**, 1011–1024 (2005).
195. N. Mrosovsky, S. Hattar, Impaired masking responses to light in melanopsin-knockout mice. *Chronobiol Int* **20**, 989–99 (2003).
196. S. E. Doyle, A. M. Castrucci, M. McCall, I. Provencio, M. Menaker, Nonvisual light responses in the Rpe65 knockout mouse: rod loss restores sensitivity to the melanopsin system. *Proc Natl Acad Sci U S A* **103**, 10432–7 (2006).

197. S. E. Doyle, T. Yoshikawa, H. Hillson, M. Menaker, Retinal pathways influence temporal niche. *Proc Natl Acad Sci U S A* **105**, 13133–8 (2008).
198. J. Aschoff, Masking and parametric effects of high-frequency light-dark cycles. *Jpn J Physiol* **49**, 11–8 (1999).
199. N. Mrosovsky, Masking: history, definitions, and measurement. *Chronobiol Int* **16**, 415–29 (1999).
200. U. Redlin, Neural basis and biological function of masking by light in mammals: suppression of melatonin and locomotor activity. *Chronobiol Int* **18**, 737–58 (2001).
201. J. Aschoff, C. von Goetz, Masking of circadian activity rhythms in hamsters by darkness. *J Comp Physiol A* **162**, 559–62 (1988).
202. S. Daan, Tonic and phasic effects of light in the entrainment of circadian rhythms. *Ann N Y Acad Sci* **290**, 51–9 (1977).
203. D. S. McNeill, C. M. Altimus, S. Hattar, Retina-clock relations dictate nocturnal to diurnal behaviors. *Proc Natl Acad Sci U S A* **105**, 12645–6 (2008).
204. J. L. Kavanau, Influences of light on activity of small mammals. *Ecology* **50**, 548–557 (1969).
205. J. H. Meijer, G. A. Groos, B. Rusak, Luminance coding in a circadian pacemaker: the suprachiasmatic nucleus of the rat and the hamster. *Brain Research* **382**, 109–118 (1986).
206. Y. Y. Jiao, T. M. Lee, B. Rusak, Photoc responses of suprachiasmatic area neurons in diurnal degus (*Octodon degus*) and nocturnal rats (*Rattus norvegicus*). *Brain Research* **817**, 93–103 (1999).
207. G. A. Groos, R. Mason, The visual properties of rat and cat suprachiasmatic neurons. *Journal of Comparative Physiology* **135**, 349–356 (1980).
208. T. J. Nakamura, K. Fujimura, S. Ebihara, K. Shinohara, Light response of the neuronal firing activity in the suprachiasmatic nucleus of mice. *Neuroscience Letters* **371**, 244–248 (2004).
209. Y. Sawaki, Suprachiasmatic nucleus neurones: excitation and inhibition mediated by the direct retino-hypothalamic projection in female rats. *Exp Brain Res* **37**, 127–38 (1979).
210. E. Drouyer, C. Rieux, R. a Hut, H. M. Cooper, Responses of suprachiasmatic nucleus neurons to light and dark adaptation: relative contributions of melanopsin and rod-cone inputs. *J Neurosci* **27**, 9623–9631 (2007).
211. L. S. Mure, C. Rieux, S. Hattar, H. M. Cooper, Melanopsin-dependent nonvisual responses: evidence for photopigment bistability in vivo. *J Biol Rhythms* **22**, 411–424 (2007).
212. J. H. Meijer, K. Watanabe, J. Schaap, H. Albus, L. Détári, Light responsiveness of the suprachiasmatic nucleus: long-term multiunit and single-unit recordings in freely moving rats. *J Neurosci* **18**, 9078–9087 (1998).
213. Y.-Y. Jiao, B. Rusak, Electrophysiology of optic nerve input to suprachiasmatic nucleus neurons in rats and degus. *Brain Res* **960**, 142–51 (2003).
214. J. R. Wilson, A. Cowey, P. Somogy, GABA immunopositive axons in the optic nerve and optic tract of macaque monkeys. *Vision Res* **36**, 1357–63 (1996).

215. A. J. Gall, D. D. Shuboni, L. Yan, A. A. Nunez, L. Smale, Suprachiasmatic Nucleus and Subparaventricular Zone Lesions Disrupt Circadian Rhythmicity but Not Light-Induced Masking Behavior in Nile Grass Rats. *J Biol Rhythms* **31**, 170–81 (2016).
216. M. H. Hastings, A. C. Roberts, J. Herbert, Neurotoxic lesions of the anterior hypothalamus disrupt the photoperiodic but not the circadian system of the Syrian hamster. *Neuroendocrinology* **40**, 316–24 (1985).
217. S. Honma, *et al.*, Suprachiasmatic nucleus: Cellular clocks and networks. *Progress in Brain Research* **199**, 129–141 (2012).
218. S. Honma, W. Nakamura, T. Shirakawa, K. Honma, Diversity in the circadian periods of single neurons of the rat suprachiasmatic nucleus depends on nuclear structure and intrinsic period. *Neurosci Lett* **358**, 173–6 (2004).
219. D. K. Welsh, J. S. Takahashi, S. A. Kay, Suprachiasmatic nucleus: cell autonomy and network properties. *Annu Rev Physiol* **72**, 551–77 (2010).
220. J. A. Mohawk, J. S. Takahashi, Cell autonomy and synchrony of suprachiasmatic nucleus circadian oscillators. *Trends Neurosci* **34**, 349–58 (2011).
221. J. H. Meijer, S. Michel, H. T. Vanderleest, J. H. T. Rohling, Daily and seasonal adaptation of the circadian clock requires plasticity of the SCN neuronal network. *Eur J Neurosci* **32**, 2143–51 (2010).
222. S. Yamaguchi, *et al.*, Synchronization of cellular clocks in the suprachiasmatic nucleus. *Science* **302**, 1408–12 (2003).
223. H. Okamura, Integration of mammalian circadian clock signals: from molecule to behavior. *J Endocrinol* **177**, 3–6 (2003).
224. J. A. Evans, Collective timekeeping among cells of the master circadian clock. *J Endocrinol* **230**, R27–49 (2016).
225. A. Ramkisoensing, J. H. Meijer, Synchronization of Biological Clock Neurons by Light and Peripheral Feedback Systems Promotes Circadian Rhythms and Health. *Front Neurol* **6**, 128 (2015).
226. T. M. Brown, H. D. Piggins, Spatiotemporal heterogeneity in the electrical activity of suprachiasmatic nuclei neurons and their response to photoperiod. *J Biol Rhythms* **24**, 44–54 (2009).
227. J. Rohling, L. Wolters, J. H. Meijer, Simulation of day-length encoding in the SCN: from single-cell to tissue-level organization. *J Biol Rhythms* **21**, 301–313 (2006).
228. J. Rohling, J. H. Meijer, H. T. VanderLeest, J. Admiraal, Phase differences between SCN neurons and their role in photoperiodic encoding; a simulation of ensemble patterns using recorded single unit electrical activity patterns. *Journal of Physiology Paris* **100**, 261–270 (2006).
229. C. S. Colwell, Rhythmic coupling among cells in the suprachiasmatic nucleus. *Journal of Neurobiology* **43**, 379–388 (2000).
230. M.-H. Wang, N. Chen, J.-H. Wang, The coupling features of electrical synapses modulate neuronal synchrony in hypothalamic superachiasmatic nucleus. *Brain Res* **1550**, 9–17 (2014).
231. D. K. Welsh, S. M. Reppert, Gap junctions couple astrocytes but not neurons in dissociated cultures of rat suprachiasmatic nucleus. *Brain Res* **706**, 30–6 (1996).

232. Z. G. Jiang, Y. Q. Yang, C. N. Allen, Tracer and electrical coupling of rat suprachiasmatic nucleus neurons. *Neuroscience* **77**, 1059–66 (1997).
233. A. N. van den Pol, F. E. Dudek, Cellular communication in the circadian clock, the suprachiasmatic nucleus. *Neuroscience* **56**, 793–811 (1993).
234. S. Michel, C. S. Colwell, Cellular communication and coupling within the suprachiasmatic nucleus. *Chronobiol Int* **18**, 579–600 (2001).
235. E. S. Maywood, *et al.*, Synchronization and maintenance of timekeeping in suprachiasmatic circadian clock cells by neuropeptidergic signaling. *Curr Biol* **16**, 599–605 (2006).
236. S. J. Aton, E. D. Herzog, Come together, right...now: synchronization of rhythms in a mammalian circadian clock. *Neuron* **48**, 531–4 (2005).
237. R. Y. Moore, J. C. Speh, R. K. Leak, Suprachiasmatic nucleus organization. *Cell Tissue Res* **309**, 89–98 (2002).
238. E. S. Maywood, J. E. Chesham, J. A. O'Brien, M. H. Hastings, A diversity of paracrine signals sustains molecular circadian cycling in suprachiasmatic nucleus circuits. *Proc Natl Acad Sci U S A* **108**, 14306–11 (2011).
239. A. J. Harmar, An essential role for peptidergic signalling in the control of circadian rhythms in the suprachiasmatic nuclei. *J Neuroendocrinol* **15**, 335–8 (2003).
240. H. Albus, M. J. Vansteensel, S. Michel, G. D. Block, J. H. Meijer, A GABAergic mechanism is necessary for coupling dissociable ventral and dorsal regional oscillators within the circadian clock. *Current Biology* **15**, 886–893 (2005).
241. R. Y. Moore, J. C. Speh, GABA is the principal neurotransmitter of the circadian system. *Neurosci Lett* **150**, 112–6 (1993).
242. S. Wagner, M. Castel, H. Gainer, Y. Yarom, GABA in the mammalian suprachiasmatic nucleus and its role in diurnal rhythmicity. *Nature* **387**, 598–603 (1997).
243. C. Liu, S. M. Reppert, GABA synchronizes clock cells within the suprachiasmatic circadian clock. *Neuron* **25**, 123–8 (2000).
244. S. J. Aton, C. S. Colwell, A. J. Harmar, J. Waschek, E. D. Herzog, Vasoactive intestinal polypeptide mediates circadian rhythmicity and synchrony in mammalian clock neurons. *Nat Neurosci* **8**, 476–83 (2005).
245. A. J. Harmar, *et al.*, The VPAC(2) receptor is essential for circadian function in the mouse suprachiasmatic nuclei. *Cell* **109**, 497–508 (2002).
246. K. L. Gamble, G. C. Allen, T. Zhou, D. G. McMahon, Gastrin-releasing peptide mediates light-like resetting of the suprachiasmatic nucleus circadian pacemaker through cAMP response element-binding protein and Per1 activation. *J Neurosci* **27**, 12078–12087 (2007).
247. M. C. Antle, L. J. Kriegsfeld, R. Silver, Signaling within the master clock of the brain: localized activation of mitogen-activated protein kinase by gastrin-releasing peptide. *J Neurosci* **25**, 2447–54 (2005).
248. A. Kalsbeek, E. Fliers, M. A. Hofman, D. F. Swaab, R. M. Buijs, Vasopressin and the output of the hypothalamic biological clock. *J Neuroendocrinol* **22**, 362–72 (2010).
249. R. Y. Moore, R. Silver, Suprachiasmatic nucleus organization. *Chronobiol Int* **15**, 475–87 (1998).

250. I. Lorén, *et al.*, Distribution of vasoactive intestinal polypeptide in the rat and mouse brain. *Neuroscience* **4**, 1953–76 (1979).
251. E. G. Stopa, *et al.*, Localization of vasoactive intestinal peptide and peptide histidine isoleucine immunoreactivity and mRNA within the rat suprachiasmatic nucleus. *Brain Res* **464**, 319–25 (1988).
252. J. P. Card, R. Y. Moore, Organization of lateral geniculate-hypothalamic connections in the rat. *J Comp Neurol* **284**, 135–47 (1989).
253. M. Lokshin, J. LeSauter, R. Silver, Selective Distribution of Retinal Input to Mouse SCN Revealed in Analysis of Sagittal Sections. *J Biol Rhythms* **30**, 251–7 (2015).
254. A. Vosko, *et al.*, Role of vasoactive intestinal peptide in the light input to the circadian system. *Eur J Neurosci* **42**, 1839–48 (2015).
255. H. E. Albers, N. Minamitani, E. Stopa, C. F. Ferris, Light selectively alters vasoactive intestinal peptide and peptide histidine isoleucine immunoreactivity within the rat suprachiasmatic nucleus. *Brain Res* **437**, 189–92 (1987).
256. Y. Isobe, H. Nishino, Vasoactive intestinal peptide and gastrin-releasing peptide play distinct roles in the suprachiasmatic nucleus. *Brain Res Bull* **40**, 287–90 (1996).
257. T.-L. To, M. A. Henson, E. D. Herzog, F. J. Doyle, A molecular model for intercellular synchronization in the mammalian circadian clock. *Biophys J* **92**, 3792–803 (2007).
258. H. D. Piggins, D. J. Cutler, The roles of vasoactive intestinal polypeptide in the mammalian circadian clock. *J Endocrinol* **177**, 7–15 (2003).
259. A. J. McArthur, *et al.*, Gastrin-releasing peptide phase-shifts suprachiasmatic nuclei neuronal rhythms in vitro. *J Neurosci* **20**, 5496–502 (2000).
260. R. Aida, *et al.*, Gastrin-releasing peptide mediates photic entrainable signals to dorsal subsets of suprachiasmatic nucleus via induction of Period gene in mice. *Mol Pharmacol* **61**, 26–34 (2002).
261. W. Nakamura, S. Honma, T. Shirakawa, K. Honma, Regional pacemakers composed of multiple oscillator neurons in the rat suprachiasmatic nucleus. *Eur J Neurosci* **14**, 666–74 (2001).
262. H. Dardente, V.-J. Poirel, P. Klosen, P. Pévet, M. Masson-Pévet, Per and neuropeptide expression in the rat suprachiasmatic nuclei: compartmentalization and differential cellular induction by light. *Brain Res* **958**, 261–71 (2002).
263. J. A. Evans, *et al.*, Shell neurons of the master circadian clock coordinate the phase of tissue clocks throughout the brain and body. *BMC Biol* **13**, 43 (2015).
264. S. Yamazaki, *et al.*, Resetting central and peripheral circadian oscillators in transgenic rats. *Science* **288**, 682–5 (2000).
265. A. Balsalobre, *et al.*, Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science* **289**, 2344–7 (2000).
266. C. Dibner, U. Schibler, U. Albrecht, The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol* **72**, 517–49 (2010).
267. X. Jin, *et al.*, A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. *Cell* **96**, 57–68 (1999).

268. M. Mieda, *et al.*, Cellular clocks in AVP neurons of the SCN are critical for interneuronal coupling regulating circadian behavior rhythm. *Neuron* **85**, 1103–16 (2015).
269. Y. Yamaguchi, *et al.*, Mice genetically deficient in vasopressin V1a and V1b receptors are resistant to jet lag. *Science* **342**, 85–90 (2013).
270. S. J. Aton, J. E. Huettnner, M. Straume, E. D. Herzog, GABA and Gi/o differentially control circadian rhythms and synchrony in clock neurons. *Proc Natl Acad Sci U S A* **103**, 19188–93 (2006).
271. R. Cohen, N. Kronfeld-Schor, C. Ramanathan, A. Baumgras, L. Smale, The substructure of the suprachiasmatic nucleus: Similarities between nocturnal and diurnal spiny mice. *Brain Behav Evol* **75**, 9–22 (2010).
272. L. Pinato, R. Frazão, R. J. Cruz-Rizzolo, J. S. Cavalcante, M. I. Nogueira, Immunocytochemical characterization of the pregeniculate nucleus and distribution of retinal and neuropeptide Y terminals in the suprachiasmatic nucleus of the Cebus monkey. *J Chem Neuroanat* **37**, 207–13 (2009).
273. R. J. Lucas, F. R. Cagampang, A. S. Loudon, J. A. Stirling, C. W. Coen, Expression of vasoactive intestinal peptide mRNA in the suprachiasmatic nuclei of the circadian tau mutant hamster. *Neurosci Lett* **249**, 147–50 (1998).
274. H. Dardente, *et al.*, Daily and circadian expression of neuropeptides in the suprachiasmatic nuclei of nocturnal and diurnal rodents. *Brain Res Mol Brain Res* **124**, 143–51 (2004).
275. K. Shinohara, K. Tominaga, Y. Isobe, S. T. Inouye, Photoc regulation of peptides located in the ventrolateral subdivision of the suprachiasmatic nucleus of the rat: daily variations of vasoactive intestinal polypeptide, gastrin-releasing peptide, and neuropeptide Y. *J Neurosci* **13**, 793–800 (1993).
276. M. M. Mahoney, *et al.*, Daily rhythms and sex differences in vasoactive intestinal polypeptide, VIPR2 receptor and arginine vasopressin mRNA in the suprachiasmatic nucleus of a diurnal rodent, *Arvicantis niloticus*. *Eur J Neurosci* **30**, 1537–43 (2009).
277. K. Krajnak, M. L. Kashon, K. L. Rosewell, P. M. Wise, Sex differences in the daily rhythm of vasoactive intestinal polypeptide but not arginine vasopressin messenger ribonucleic acid in the suprachiasmatic nuclei. *Endocrinology* **139**, 4189–96 (1998).
278. M. A. Hofman, J. N. Zhou, D. F. Swaab, No evidence for a diurnal vasoactive intestinal polypeptide (VIP) rhythm in the human suprachiasmatic nucleus. *Brain Res* **722**, 78–82 (1996).
279. H. Abe, S. Honma, K. Shinohara, K. I. Honma, Circadian modulation in photic induction of Fos-like immunoreactivity in the suprachiasmatic nucleus cells of diurnal chipmunk, *Eutamias asiaticus*. *J Comp Physiol A* **176**, 159–67 (1995).
280. K. Krajnak, L. Dickenson, T. M. Lee, The induction of Fos-like proteins in the suprachiasmatic nuclei and intergeniculate leaflet by light pulses in degus (*Octodon degus*) and rats. *J Biol Rhythms* **12**, 401–12 (1997).
281. M. A. Rea, Light increases Fos-related protein immunoreactivity in the rat suprachiasmatic nuclei. *Brain Res Bull* **23**, 577–81 (1989).
282. B. Rusak, H. A. Robertson, W. Wisden, S. P. Hunt, Light pulses that shift rhythms induce gene expression in the suprachiasmatic nucleus. *Science* **248**, 1237–40 (1990).
283. N. Aronin, S. M. Sagar, F. R. Sharp, W. J. Schwartz, Light regulates expression of a Fos-related protein in rat suprachiasmatic nuclei. *Proc Natl Acad Sci U S A* **87**, 5959–62 (1990).

284. J. M. Kornhauser, D. E. Nelson, K. E. Mayo, J. S. Takahashi, Photic and circadian regulation of c-fos gene expression in the hamster suprachiasmatic nucleus. *Neuron* **5**, 127–34 (1990).
285. C. Katona, S. Rose, L. Smale, The expression of Fos within the suprachiasmatic nucleus of the diurnal rodent *Arvicanthis niloticus*. *Brain Res* **791**, 27–34 (1998).
286. C. S. Colwell, R. G. Foster, Photic regulation of Fos-like immunoreactivity in the suprachiasmatic nucleus of the mouse. *J Comp Neurol* **324**, 135–42 (1992).
287. B. Rusak, L. McNaughton, H. A. Robertson, S. P. Hunt, Circadian variation in photic regulation of immediate-early gene mRNAs in rat suprachiasmatic nucleus cells. *Brain Res Mol Brain Res* **14**, 124–30 (1992).
288. M. E. Guido, D. Goguen, L. De Guido, H. A. Robertson, B. Rusak, Circadian and photic regulation of immediate-early gene expression in the hamster suprachiasmatic nucleus. *Neuroscience* **90**, 555–71 (1999).
289. D. J. Earnest, S. DiGiorgio, J. A. Olschowka, Light induces expression of fos-related proteins within gastrin-releasing peptide neurons in the rat suprachiasmatic nucleus. *Brain Res* **627**, 205–9 (1993).
290. J. D. Mikkelsen, *et al.*, A dual-immunocytochemical method to localize c-fos protein in specific neurons based on their content of neuropeptides and connectivity. *Histochemistry* **101**, 245–51 (1994).
291. I. N. Karatsoreos, L. Yan, J. LeSauter, R. Silver, Phenotype matters: identification of light-responsive cells in the mouse suprachiasmatic nucleus. *J Neurosci* **24**, 68–75 (2004).
292. M. Tanaka, *et al.*, Direct retinal projections to GRP neurons in the suprachiasmatic nucleus of the rat. *Neuroreport* **8**, 2187–91 (1997).
293. J. M. Franci, G. Kaur, J. D. Glass, Roles of light and serotonin in the regulation of gastrin-releasing peptide and arginine vasopressin output in the hamster SCN circadian clock. *Eur J Neurosci* **32**, 1170–9 (2010).
294. S. Rose, C. M. Novak, M. M. Mahoney, A. A. Nunez, L. Smale, Fos expression within vasopressin-containing neurons in the suprachiasmatic nucleus of diurnal rodents compared to nocturnal rodents. *J Biol Rhythms* **14**, 37–46 (1999).
295. H. J. Romijn, A. A. Sluiter, C. W. Pool, J. Wortel, R. M. Buijs, Differences in colocalization between Fos and PHI, GRP, VIP and VP in neurons of the rat suprachiasmatic nucleus after a light stimulus during the phase delay versus the phase advance period of the night. *J Comp Neurol* **372**, 1–8 (1996).
296. M. M. Mahoney, A. A. Nunez, L. Smale, Calbindin and Fos within the suprachiasmatic nucleus and the adjacent hypothalamus of *Arvicanthis niloticus* and *Rattus norvegicus*. *Neuroscience* **99**, 565–575 (2000).
297. J. E. Quintero, S. J. Kuhlman, D. G. McMahon, The biological clock nucleus: a multiphasic oscillator network regulated by light. *J Neurosci* **23**, 8070–6 (2003).
298. A. Jagota, H. O. de la Iglesia, W. J. Schwartz, Morning and evening circadian oscillations in the suprachiasmatic nucleus in vitro. *Nat Neurosci* **3**, 372–6 (2000).
299. N. Inagaki, S. Honma, D. Ono, Y. Tanahashi, K. Honma, Separate oscillating cell groups in mouse suprachiasmatic nucleus couple photoperiodically to the onset and end of daily activity. *Proc Natl Acad Sci U S A* **104**, 7664–9 (2007).

300. M. C. Antle, R. Silver, Orchestrating time: arrangements of the brain circadian clock. *Trends Neurosci* **28**, 145–51 (2005).
301. A. Kalsbeek, S. Perreau-Lenz, R. M. Buijs, A network of (autonomic) clock outputs. *Chronobiol Int* **23**, 521–35 (2006).
302. R. Silver, W. J. Schwartz, The suprachiasmatic nucleus is a functionally heterogeneous timekeeping organ. *Methods Enzymol* **393**, 451–65 (2005).
303. M. D. C. Belle, C. O. Diekman, D. B. Forger, H. D. Piggins, Daily electrical silencing in the mammalian circadian clock. *Science* **326**, 281–4 (2009).
304. J. Schaap, *et al.*, Heterogeneity of rhythmic suprachiasmatic nucleus neurons: Implications for circadian waveform and photoperiodic encoding. *Proc Natl Acad Sci U S A* **100**, 15994–9 (2003).
305. L. P. Morin, K.-Y. Shivers, J. H. Blanchard, L. Muscat, Complex organization of mouse and rat suprachiasmatic nucleus. *Neuroscience* **137**, 1285–97 (2006).
306. L. P. Morin, SCN organization reconsidered. *J Biol Rhythms* **22**, 3–13 (2007).
307. K. Saeb-Parsy, R. E. J. Dyball, Defined cell groups in the rat suprachiasmatic nucleus have different day/night rhythms of single-unit activity in vivo. *J Biol Rhythms* **18**, 26–42 (2003).
308. S. Daan, The Colin S. Pittendrigh Lecture. Colin Pittendrigh, Jürgen Aschoff, and the natural entrainment of circadian systems. *J Biol Rhythms* **15**, 195–207 (2000).
309. D. G. M. Beersma, B. A. D. van Bunnik, R. A. Hut, S. Daan, Emergence of circadian and photoperiodic system level properties from interactions among pacemaker cells. *J Biol Rhythms* **23**, 362–73 (2008).
310. V. K. Sharma, Period responses to Zeitgeber signals stabilize circadian clocks during entrainment. *Chronobiol Int* **20**, 389–404 (2003).
311. C. L. Ehlers, E. Frank, D. J. Kupfer, Social zeitgebers and biological rhythms. A unified approach to understanding the etiology of depression. *Arch Gen Psychiatry* **45**, 948–52 (1988).
312. A. J. Lewy, S. Ahmed, J. M. Jackson, R. L. Sack, Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int* **9**, 380–92 (1992).
313. D. E. Nelson, J. S. Takahashi, Sensitivity and integration in a visual pathway for circadian entrainment in the hamster (*Mesocricetus auratus*). *J Physiol* **439**, 115–45 (1991).
314. P. J. DECOURSEY, FUNCTION OF A LIGHT RESPONSE RHYTHM IN HAMSTERS. *J Cell Physiol* **63**, 189–96 (1964).
315. M. Mahoney, A. Bult, L. Smale, Phase response curve and light-induced fos expression in the suprachiasmatic nucleus and adjacent hypothalamus of *Arvicanthis niloticus*. *J Biol Rhythms* **16**, 149–62 (2001).
316. H. A. Sloten, S. Krekling, P. Pévet, Photic and nonphotic effects on the circadian activity rhythm in the diurnal rodent *Arvicanthis ansorgei*. *Behavioural brain research* **165**, 91–7 (2005).
317. M. J. Kas, D. M. Edgar, Photic phase response curve in *Octodon degus*: assessment as a function of activity phase preference. *Am J Physiol Regul Integr Comp Physiol* **278**, R1385-9 (2000).
318. D. Kumar, M. Singaravel, Phase and period responses to short light pulses in a wild diurnal rodent, *Funambulus pennanti*. *Chronobiol Int* **31**, 320–7 (2014).

319. M. E. Jewett, *et al.*, Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. *Am J Physiol* **273**, R1800-9 (1997).
320. M. A. St Hilaire, *et al.*, Human phase response curve to a 1 h pulse of bright white light. *J Physiol* **590**, 3035–45 (2012).
321. D. G. Beersma, S. Daan, R. A. Hut, Accuracy of circadian entrainment under fluctuating light conditions: contributions of phase and period responses. *J Biol Rhythms* **14**, 320–9 (1999).
322. R. El Moussaoui, N. Bouhaddou, M. Sabbar, H. M. Cooper, N. Lakhdar-Ghazal, Phase and period responses of the jerboa *Jaculus orientalis* to short light pulses. *Chronobiol Int* **27**, 1348–64 (2010).
323. V. K. Sharma, S. Daan, Circadian phase and period responses to light stimuli in two nocturnal rodents. *Chronobiol Int* **19**, 659–70 (2002).
324. A. M. Rosenwasser, S. M. Dwyer, Phase shifting the hamster circadian clock by 15-minute dark pulses. *J Biol Rhythms* **17**, 238–47 (2002).
325. J. Mendoza, F. G. Revel, P. Pévet, E. Challet, Shedding light on circadian clock resetting by dark exposure: differential effects between diurnal and nocturnal rodents. *Eur J Neurosci* **25**, 3080–90 (2007).
326. R. Bartoszewicz, G. Barbacka-Surowiak, Serotonin increases the phase shift of the circadian locomotor activity rhythm in mice after dark pulses in constant light conditions. *Folia Biol (Praha)* **55**, 101–8 (2007).
327. J. Mendoza, D. Clesse, P. Pévet, E. Challet, Serotonergic potentiation of dark pulse-induced phase-shifting effects at midday in hamsters. *J Neurochem* **106**, 1404–14 (2008).
328. J. Aschoff, Circadian rhythms: influences of internal and external factors on the period measured in constant conditions. *Zeitschrift für Tierpsychologie* **49**, 225–249 (1979).
329. P. J. DeCoursey, LD ratios and the entrainment of circadian activity in a nocturnal and a diurnal rodent. *Journal of Comparative Physiology* **78**, 221–235 (1972).
330. H. Ohta, S. Yamazaki, D. G. McMahon, Constant light desynchronizes mammalian clock neurons. *Nat Neurosci* **8**, 267–269 (2005).
331. S. Daan, C. S. Pittendrigh, A functional analysis of circadian pacemakers in nocturnal rodents - III. Heavy water and constant light: Homeostasis of frequency? *Journal of Comparative Physiology* **106**, 267–290 (1976).
332. R. Refinetti, *Circadian Physiology*, Second Edi (CRC Press, Taylor & Francis Group, 2006).
333. K. I. Honma, T. Hiroshige, Endogenous ultradian rhythms in rats exposed to prolonged continuous light. *Am J Physiol* **235**, R250-6 (1978).
334. M. H. Hagenauer, T. M. Lee, Circadian organization of the diurnal Caviomorph rodent, *Octodon degus*. *Biological Rhythm Research* **39**, 269–289 (2008).
335. B. M. Tomotani, *et al.*, Field and laboratory studies provide insights into the meaning of day-time activity in a subterranean rodent (*Ctenomys aff. knighti*), the tuco-tuco. *PLoS One* **7**, e37918 (2012).
336. C. A. Shibuya, R. B. Melnyk, N. Mrosovsky, Simultaneous splitting of drinking and locomotor activity rhythms in a golden hamster. *Naturwissenschaften* **67**, 45–7 (1980).

337. G. E. Pickard, R. Kahn, R. Silver, Splitting of the circadian rhythm of body temperature in the golden hamster. *Physiol Behav* **32**, 763–6 (1984).
338. J. M. Swann, F. W. Turek, Multiple circadian oscillators regulate the timing of behavioral and endocrine rhythms in female golden hamsters. *Science* **228**, 898–900 (1985).
339. R. Mason, The effects of continuous light exposure on Syrian hamster suprachiasmatic (SCN) neuronal discharge activity in vitro. *Neurosci Lett* **123**, 160–3 (1991).
340. P. Zlomanczuk, R. R. Margraf, G. R. Lynch, In vitro electrical activity in the suprachiasmatic nucleus following splitting and masking of wheel-running behavior. *Brain Res* **559**, 94–9 (1991).
341. Z. Boulos, M. Terman, Splitting of circadian rhythms in the rat. *Journal of Comparative Physiology* **134**, 75–83 (1979).
342. R. H. Swade, C. S. Pittendrigh, Circadian locomotor rhythms of rodents in the arctic. *American Naturalist* **101**, 431–466 (1967).
343. H. Pohl, Die Aktivitätsperiodik von zwei tagaktiven Nagern, *Funambulus palmarum* und *Eutamias sibiricus* unter Dauerlichtbedingungen. *Journal of Comparative Physiology* **78**, 60–74 (1972).
344. H. O. de la Iglesia, J. Meyer, A. Carpino, W. J. Schwartz, Antiphase oscillation of the left and right suprachiasmatic nuclei. *Science* **290**, 799–801 (2000).
345. G. E. Pickard, F. W. Turek, Splitting of the circadian rhythm of activity is abolished by unilateral lesions of the suprachiasmatic nuclei. *Science* **215**, 1119–21 (1982).
346. L. Yan, N. C. Foley, J. M. Bobula, L. J. Kriegsfeld, R. Silver, Two antiphase oscillations occur in each suprachiasmatic nucleus of behaviorally split hamsters. *J Neurosci* **25**, 9017–26 (2005).
347. M. P. Butler, M. N. Rainbow, E. Rodriguez, S. M. Lyon, R. Silver, Twelve-hour days in the brain and behavior of split hamsters. *Eur J Neurosci* **36**, 2556–66 (2012).
348. F. C. Davis, R. A. Gorski, UNILATERAL LESIONS OF THE HAMSTER SUPRACHIASMATIC NUCLEI - EVIDENCE FOR REDUNDANT CONTROL OF CIRCADIAN-RHYTHMS. *Journal of Comparative Physiology* **154**, 221–232 (1984).
349. S. Daan, C. Berde, Two coupled oscillators: simulations of the circadian pacemaker in mammalian activity rhythms. *J Theor Biol* **70**, 297–313 (1978).
350. M. Kawato, R. Suzuki, Two coupled neural oscillators as a model of the circadian pacemaker. *J Theor Biol* **86**, 547–75 (1980).
351. G. A. Oda, W. O. Friesen, A model for “splitting” of running-wheel activity in hamsters. *J Biol Rhythms* **17**, 76–88 (2002).
352. D. J. Earnest, F. W. Turek, SPLITTING OF THE CIRCADIAN-RHYTHM OF ACTIVITY IN HAMSTERS - EFFECTS OF EXPOSURE TO CONSTANT DARKNESS AND SUBSEQUENT RE-EXPOSURE TO CONSTANT LIGHT. *Journal of Comparative Physiology* **145**, 405–411 (1982).
353. J. A. Evans, M. R. Gorman, In synch but not in step: Circadian clock circuits regulating plasticity in daily rhythms. *Neuroscience* **320**, 259–80 (2016).
354. M. Mrugala, P. Zlomanczuk, A. Jagota, W. J. Schwartz, Rhythmic multiunit neural activity in slices of hamster suprachiasmatic nucleus reflect prior photoperiod. *Am J Physiol Regul Integr Comp Physiol* **278**, R987–94 (2000).

355. H. T. vanderLeest, J. H. T. Rohling, S. Michel, J. H. Meijer, Phase shifting capacity of the circadian pacemaker determined by the SCN neuronal network organization. *PLoS One* **4**, e4976 (2009).
356. A. Ramkisoensing, *et al.*, Enhanced phase resetting in the synchronized suprachiasmatic nucleus network. *J Biol Rhythms* **29**, 4–15 (2014).
357. A. Ramkisoensing, E. Challet, D. Ciocca, J. H. Meijer, Temporal organization of behavioural activity by the SCN in the diurnal grass rat *Arvicanthis ansorgei*. *In preparation*.
358. G. Leach, C. Ramanathan, J. Langel, L. Yan, Responses of brain and behavior to changing day-length in the diurnal grass rat (*Arvicanthis niloticus*). *Neuroscience* **234**, 31–9 (2013).
359. A. Kalsbeek, R. M. Buijs, Output pathways of the mammalian suprachiasmatic nucleus: coding circadian time by transmitter selection and specific targeting. *Cell Tissue Res* **309**, 109–18 (2002).
360. R. Y. Moore, R. L. Danchenko, Paraventricular-subparaventricular hypothalamic lesions selectively affect circadian function. *Chronobiol Int* **19**, 345–60 (2002).
361. S. Perreau-Lenz, P. Pévet, R. M. Buijs, A. Kalsbeek, The biological clock: the bodyguard of temporal homeostasis. *Chronobiol Int* **21**, 1–25 (2004).
362. A. Kalsbeek, *et al.*, SCN outputs and the hypothalamic balance of life. *J Biol Rhythms* **21**, 458–69 (2006).
363. A. Kalsbeek, J. van der Vliet, R. M. Buijs, Decrease of endogenous vasopressin release necessary for expression of the circadian rise in plasma corticosterone: a reverse microdialysis study. *J Neuroendocrinol* **8**, 299–307 (1996).
364. J.-D. Li, K. J. Burton, C. Zhang, S.-B. Hu, Q.-Y. Zhou, Vasopressin receptor V1a regulates circadian rhythms of locomotor activity and expression of clock-controlled genes in the suprachiasmatic nuclei. *Am J Physiol Regul Integr Comp Physiol* **296**, R824–30 (2009).
365. M. H. Brown, A. A. Nunez, Vasopressin-deficient rats show a reduced amplitude of the circadian sleep rhythm. *Physiol Behav* **46**, 759–62 (1989).
366. A. Kalsbeek, *et al.*, Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. *Eur J Neurosci* **12**, 3146–54 (2000).
367. R. M. Buijs, Y. X. Hou, S. Shinn, L. P. Renaud, Ultrastructural evidence for intra- and extranuclear projections of GABAergic neurons of the suprachiasmatic nucleus. *J Comp Neurol* **340**, 381–91 (1994).
368. M. L. Hermes, E. M. Coderre, R. M. Buijs, L. P. Renaud, GABA and glutamate mediate rapid neurotransmission from suprachiasmatic nucleus to hypothalamic paraventricular nucleus in rat. *J Physiol*, 749–57 (1996).
369. D. H. Loh, C. Abad, C. S. Colwell, J. A. Waschek, Vasoactive intestinal peptide is critical for circadian regulation of glucocorticoids. *Neuroendocrinology* **88**, 246–55 (2008).
370. M. Y. Cheng, *et al.*, Prokineticin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. *Nature* **417**, 405–10 (2002).
371. Q.-Y. Zhou, M. Y. Cheng, Prokineticin 2 and circadian clock output. *FEBS J* **272**, 5703–9 (2005).
372. A. Kramer, *et al.*, Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling. *Science* **294**, 2511–5 (2001).

373. A. Kramer, *et al.*, Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signalling. *Novartis Found Symp* **253**, 250–62; discussion 102–9, 263–6, 281–4 (2003).
374. S. Kraves, C. J. Weitz, A role for cardiotrophin-like cytokine in the circadian control of mammalian locomotor activity. *Nat Neurosci* **9**, 212–9 (2006).
375. A. Kalsbeek, *et al.*, Opposite actions of hypothalamic vasopressin on circadian corticosterone rhythm in nocturnal versus diurnal species. *European Journal of Neuroscience* **27**, 818–827 (2008).
376. J.-D. Li, W.-P. Hu, Q.-Y. Zhou, The circadian output signals from the suprachiasmatic nuclei. *Prog Brain Res* **199**, 119–27 (2012).
377. C. M. Lambert, K. K. Machida, L. Smale, A. A. Nunez, D. R. Weaver, Analysis of the prokineticin 2 system in a diurnal rodent, the unstriped Nile grass rat (*Arvicanthis niloticus*). *J Biol Rhythms* **20**, 206–18 (2005).
378. B. B. Tournier, H. Dardente, P. Vuillez, P. Pévet, E. Challet, Expression of Tgfa1 in the suprachiasmatic nuclei of nocturnal and diurnal rodents. *Neuroscience* **145**, 1138–43 (2007).
379. N. Mrosovsky, Beyond the suprachiasmatic nucleus. *Chronobiol Int* **20**, 1–8 (2003).
380. M. D. Schwartz, A. A. Nuñez, L. Smale, Rhythmic cFos expression in the ventral subparaventricular zone influences general activity rhythms in the Nile grass rat, *Arvicanthis niloticus*. *Chronobiol Int* **26**, 1290–306 (2009).
381. J. Dai, D. F. Swaab, J. Van der Vliet, R. M. Buijs, Postmortem tracing reveals the organization of hypothalamic projections of the suprachiasmatic nucleus in the human brain. *J Comp Neurol* **400**, 87–102 (1998).
382. M. D. Schwartz, H. F. Urbanski, A. A. Nunez, L. Smale, Projections of the suprachiasmatic nucleus and ventral subparaventricular zone in the Nile grass rat (*Arvicanthis niloticus*). *Brain Res* **1367**, 146–61 (2011).
383. C. M. Novak, J. A. Harris, L. Smale, A. A. Nunez, Suprachiasmatic nucleus projections to the paraventricular thalamic nucleus in nocturnal rats (*Rattus norvegicus*) and diurnal Nile grass rats (*Arvicanthis niloticus*). *Brain Res* **874**, 147–57 (2000).
384. M. M. Mahoney, L. Smale, Arginine vasopressin and vasoactive intestinal polypeptide fibers make appositions with gonadotropin-releasing hormone and estrogen receptor cells in the diurnal rodent *Arvicanthis niloticus*. *Brain Res* **1049**, 156–64 (2005).
385. E. E. Abrahamson, R. Y. Moore, Lesions of suprachiasmatic nucleus efferents selectively affect rest-activity rhythm. *Mol Cell Endocrinol* **252**, 46–56 (2006).
386. A. G. Watts, L. W. Swanson, G. Sanchez-Watts, Efferent projections of the suprachiasmatic nucleus: I. Studies using anterograde transport of Phaseolus vulgaris leucoagglutinin in the rat. *J Comp Neurol* **258**, 204–29 (1987).
387. A. G. Watts, L. W. Swanson, Efferent projections of the suprachiasmatic nucleus: II. Studies using retrograde transport of fluorescent dyes and simultaneous peptide immunohistochemistry in the rat. *J Comp Neurol* **258**, 230–52 (1987).
388. J. Lu, *et al.*, Contrasting effects of ibotenate lesions of the paraventricular nucleus and subparaventricular zone on sleep-wake cycle and temperature regulation. *J Neurosci* **21**, 4864–74 (2001).

389. W. Nakamura, *et al.*, In vivo monitoring of circadian timing in freely moving mice. *Curr Biol* **18**, 381–5 (2008).
390. A. A. Nunez, A. Bult, T. L. McElhinny, L. Smale, Daily rhythms of Fos expression in hypothalamic targets of the suprachiasmatic nucleus in diurnal and nocturnal rodents. *J Biol Rhythms* **14**, 300–6 (1999).
391. M. D. Schwartz, A. A. Nunez, L. Smale, Differences in the suprachiasmatic nucleus and lower subparaventricular zone of diurnal and nocturnal rodents. *Neuroscience* **127**, 13–23 (2004).
392. L. Smale, C. Castleberry, A. A. Nunez, Fos rhythms in the hypothalamus of Rattus and Arvicantis that exhibit nocturnal and diurnal patterns of rhythmicity. *Brain Res* **899**, 101–5 (2001).
393. H. O. de la Iglesia, J. D. Blaustein, E. L. Bittman, The suprachiasmatic area in the female hamster projects to neurons containing estrogen receptors and GnRH. *Neuroreport* **6**, 1715–22 (1995).
394. E. M. Van der Beek, T. L. Horvath, V. M. Wiegant, R. Van den Hurk, R. M. Buijs, Evidence for a direct neuronal pathway from the suprachiasmatic nucleus to the gonadotropin-releasing hormone system: combined tracing and light and electron microscopic immunocytochemical studies. *J Comp Neurol* **384**, 569–79 (1997).
395. A. Kalsbeek, J. J. van Heerikhuize, J. Wortel, R. M. Buijs, A diurnal rhythm of stimulatory input to the hypothalamo-pituitary-adrenal system as revealed by timed intrahypothalamic administration of the vasopressin V1 antagonist. *J Neurosci* **16**, 5555–65 (1996).
396. A. Kalsbeek, S. La Fleur, C. Van Heijningen, R. M. Buijs, Suprachiasmatic GABAergic inputs to the paraventricular nucleus control plasma glucose concentrations in the rat via sympathetic innervation of the liver. *J Neurosci* **24**, 7604–13 (2004).
397. A. Kalsbeek, R. M. Buijs, J. J. van Heerikhuize, M. Arts, T. P. van der Woude, Vasopressin-containing neurons of the suprachiasmatic nuclei inhibit corticosterone release. *Brain Res* **580**, 62–7 (1992).
398. J. Lewy, T. a Wehr, F. K. Goodwin, D. a Newsome, S. P. Markey, Light suppresses melatonin secretion in humans. *Science* **210**, 1267–1269 (1980).
399. R. Y. Moore, D. C. Klein, Visual pathways and the central neural control of a circadian rhythm in pineal serotonin N-acetyltransferase activity. *Brain Res* **71**, 17–33 (1974).
400. D. C. Klein, R. Y. Moore, Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. *Brain Res* **174**, 245–62 (1979).
401. S. Perreau-Lenz, *et al.*, Suprachiasmatic control of melatonin synthesis in rats: inhibitory and stimulatory mechanisms. *Eur J Neurosci* **17**, 221–8 (2003).
402. R. Y. Moore, Neural control of the pineal gland. *Behavioural brain research* **73**, 125–30 (1996).
403. A. Kalsbeek, R. A. Cutrera, J. J. Van Heerikhuize, J. Van Der Vliet, R. M. Buijs, GABA release from suprachiasmatic nucleus terminals is necessary for the light-induced inhibition of nocturnal melatonin release in the rat. *Neuroscience* **91**, 453–61 (1999).
404. S. Perreau-Lenz, A. Kalsbeek, J. Van Der Vliet, P. Pévet, R. M. Buijs, In vivo evidence for a controlled offset of melatonin synthesis at dawn by the suprachiasmatic nucleus in the rat. *Neuroscience* **130**, 797–803 (2005).
405. A. B. Dollins, I. V Zhdanova, R. J. Wurtman, H. J. Lynch, M. H. Deng, Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci U S A* **91**, 1824–8 (1994).

406. S. R. Pandi-Perumal, *et al.*, Melatonin: Nature's most versatile biological signal? *FEBS Journal* **273**, 2813–2838 (2006).
407. D. Garfinkel, M. Laudon, D. Nof, N. Zisapel, Improvement of sleep quality in elderly people by controlled-release melatonin. *The Lancet* **346**, 541–544 (1995).
408. I. V. Zhdanova, *et al.*, Melatonin promotes sleep in three species of diurnal nonhuman primates. *Physiology and Behavior* **75**, 523–529 (2002).
409. R. Huber, T. Deboer, B. Schwierin, I. Tobler, Effect of melatonin on sleep and brain temperature in the Djungarian hamster and the rat. *Physiology and Behavior* **65**, 77–82 (1998).
410. F. Mailliet, P. Galloux, D. Poisson, Comparative effects of melatonin, zolpidem and diazepam on sleep, body temperature, blood pressure and heart rate measured by radiotelemetry in Wistar rats. *Psychopharmacology (Berl)* **156**, 417–26 (2001).
411. D. D. Shuboni, A. A. Agha, T. K. H. Groves, A. J. Gall, The contribution of the pineal gland on daily rhythms and masking in diurnal grass rats, *Arvicanthis niloticus*. *Behavioural processes* **128**, 1–8 (2016).
412. P. Vivanco, V. Ortiz, M. A. Rol, J. A. Madrid, Looking for the keys to diurnality downstream from the circadian clock: role of melatonin in a dual-phasing rodent, *Octodon degus*. *J Pineal Res* **42**, 280–90 (2007).
413. L. Martinet, I. Zucker, Role of the pineal gland in circadian organization of diurnal ground squirrels. *Physiol Behav* **34**, 799–803 (1985).
414. R. E. Watson, M. C. Langub, M. G. Engle, B. E. Maley, Estrogen-receptive neurons in the anteroventral periventricular nucleus are synaptic targets of the suprachiasmatic nucleus and peri-suprachiasmatic region. *Brain Res* **689**, 254–64 (1995).
415. T. L. McElhinny, C. L. Sisk, K. E. Holekamp, L. Smale, A morning surge in plasma luteinizing hormone coincides with elevated Fos expression in gonadotropin-releasing hormone-immunoreactive neurons in the diurnal rodent, *Arvicanthis niloticus*. *Biol Reprod* **61**, 1115–22 (1999).
416. M. M. Mahoney, C. Sisk, H. E. Ross, L. Smale, Circadian regulation of gonadotropin-releasing hormone neurons and the preovulatory surge in luteinizing hormone in the diurnal rodent, *Arvicanthis niloticus*, and in a nocturnal rodent, *Rattus norvegicus*. *Biol Reprod* **70**, 1049–54 (2004).
417. M. M. Mahoney, L. Smale, A daily rhythm in mating behavior in a diurnal murid rodent *Arvicanthis niloticus*. *Horm Behav* **47**, 8–13 (2005).
418. F. A. J. L. Scheer, C. Pirovano, E. J. W. Van Someren, R. M. Buijs, Environmental light and suprachiasmatic nucleus interact in the regulation of body temperature. *Neuroscience* **132**, 465–77 (2005).
419. R. Refinetti, M. Menaker, The circadian rhythm of body temperature. *Physiol Behav* **51**, 613–37 (1992).
420. C. B. Saper, T. E. Scammell, J. Lu, Hypothalamic regulation of sleep and circadian rhythms. *Nature* **437**, 1257–63 (2005).
421. C. M. Novak, A. A. Nunez, A sparse projection from the suprachiasmatic nucleus to the sleep active ventrolateral preoptic area in the rat. *Neuroreport* **11**, 93–6 (2000).
422. X. Sun, S. Whitefield, B. Rusak, K. Semba, Electrophysiological analysis of suprachiasmatic nucleus projections to the ventrolateral preoptic area in the rat. *Eur J Neurosci* **14**, 1257–74 (2001).

423. R. M. Buijs, A. Kalsbeek, Hypothalamic integration of central and peripheral clocks. *Nat Rev Neurosci* **2**, 521–6 (2001).
424. L. P. Morin, Neuroanatomy of the extended circadian rhythm system. *Exp Neurol* **243**, 4–20 (2013).
425. N. Mrosovsky, Locomotor activity and non-photic influences on circadian clocks. *Biol Rev Camb Philos Soc* **71**, 343–72 (1996).
426. T. Deboer, M. J. Vansteensel, L. Détári, J. H. Meijer, Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci* **6**, 1086–90 (2003).
427. N. Yamada, K. Shimoda, K. Ohi, S. Takahashi, K. Takahashi, Free-access to a running wheel shortens the period of free-running rhythm in blinded rats. *Physiol Behav* **42**, 87–91 (1988).
428. N. Yamada, K. Shimoda, K. Takahashi, S. Takahashi, Relationship between free-running period and motor activity in blinded rats. *Brain Res Bull* **25**, 115–9 (1990).
429. D. M. Edgar, C. E. Martin, W. C. Dement, Activity feedback to the mammalian circadian pacemaker: influence on observed measures of rhythm period length. *J Biol Rhythms* **6**, 185–99 (1991).
430. D. M. Edgar, W. C. Dement, Regularly scheduled voluntary exercise synchronizes the mouse circadian clock. *Am J Physiol* **261**, R928–33 (1991).
431. S. G. Reeb, N. Mrosovsky, Effects of induced wheel running on the circadian activity rhythms of Syrian hamsters: entrainment and phase response curve. *J Biol Rhythms* **4**, 39–48 (1989).
432. R. E. Mistlberger, Scheduled daily exercise or feeding alters the phase of photic entrainment in Syrian hamsters. *Physiol Behav* **50**, 1257–60 (1991).
433. J. D. Glass, S. D. Tardif, R. Clements, N. Mrosovsky, Photic and nonphotic circadian phase resetting in a diurnal primate, the common marmoset. *Am J Physiol Regul Integr Comp Physiol* **280**, R191–7 (2001).
434. J. H. Meijer, J. Schaap, K. Watanabe, H. Albus, Multiunit activity recordings in the suprachiasmatic nuclei: in vivo versus in vitro models. *Brain Res* **753**, 322–7 (1997).
435. F. van Oosterhout, *et al.*, Amplitude of the SCN clock enhanced by the behavioral activity rhythm. *PLoS One* **7**, e39693 (2012).
436. A. Ramkisoensing, *et al.*, Enhanced electrical output of the SCN clock by behavioral activity feedback in the day-active grass rat *Arvicanthis ansorgei*. *In preparation*.
437. T. L. Hickey, P. D. Spear, Retinogeniculate projections in hooded and albino rats: an autoradiographic study. *Exp Brain Res* **24**, 523–9 (1976).
438. L. P. Morin, The circadian visual system. *Brain Res Brain Res Rev* **19**, 102–27 (1994).
439. M. E. Harrington, B. Rusak, Lesions of the thalamic intergeniculate leaflet alter hamster circadian rhythms. *J Biol Rhythms* **1**, 309–25 (1986).
440. G. E. Pickard, M. R. Ralph, M. Menaker, The intergeniculate leaflet partially mediates effects of light on circadian rhythms. *J Biol Rhythms* **2**, 35–56 (1987).
441. S. M. Biello, D. Janik, N. Mrosovsky, Neuropeptide Y and behaviorally induced phase shifts. *Neuroscience* **62**, 273–9 (1994).
442. E. S. Maywood, E. Smith, S. J. Hall, M. H. Hastings, A thalamic contribution to arousal-induced, non-photic entrainment of the circadian clock of the Syrian hamster. *Eur J Neurosci* **9**, 1739–47 (1997).

443. N. Vrang, N. Mrosovsky, J. D. Mikkelsen, Afferent projections to the hamster intergeniculate leaflet demonstrated by retrograde and anterograde tracing. *Brain Res Bull* **59**, 267–88 (2003).
444. D. Janik, N. Mrosovsky, Gene expression in the geniculate induced by a nonphotic circadian phase shifting stimulus. *Neuroreport* **3**, 575–8 (1992).
445. S. Deurveilher, K. Semba, “Reciprocal connections between the suprachiasmatic nucleus and the midbrain raphe nuclei: A putative role in the circadian control of behavioral states” in *Serotonin and Sleep: Molecular Functional and Clinical Aspects*, (2008), pp. 103–129.
446. A. Hay-Schmidt, N. Vrang, P. J. Larsen, J. D. Mikkelsen, Projections from the raphe nuclei to the suprachiasmatic nucleus of the rat. *J Chem Neuroanat* **25**, 293–310 (2003).
447. R. Y. Moore, J. P. Card, Intergeniculate leaflet: an anatomically and functionally distinct subdivision of the lateral geniculate complex. *J Comp Neurol* **344**, 403–30 (1994).
448. M. E. Harrington, D. M. Nance, B. Rusak, Neuropeptide Y immunoreactivity in the hamster geniculo-suprachiasmatic tract. *Brain Res Bull* **15**, 465–72 (1985).
449. C. F. Gillespie, K. L. Huhman, T. O. Babagbemi, H. E. Albers, Bicuculline increases and muscimol reduces the phase-delaying effects of light and VIP/PHI/GRP in the suprachiasmatic region. *J Biol Rhythms* **11**, 137–44 (1996).
450. E. G. Marchant, N. V. Watson, R. E. Mistlberger, Both neuropeptide Y and serotonin are necessary for entrainment of circadian rhythms in mice by daily treadmill running schedules. *J Neurosci* **17**, 7974–87 (1997).
451. P. Pévet, *et al.*, Melatonin in the multi-oscillatory mammalian circadian world. *Chronobiol Int* **23**, 39–51 (2006).
452. P. Pevet, E. Challet, Melatonin: both master clock output and internal time-giver in the circadian clocks network. *J Physiol Paris* **105**, 170–82 (2011).
453. L. Smale, T. Mcelhinny, J. Nixon, B. Gubik, S. Rose, Patterns of wheel running are related to Fos expression in neuropeptide-Y-containing neurons in the intergeniculate leaflet of *Arvicantis niloticus*. *J Biol Rhythms* **16**, 163–72 (2001).
454. D. Janik, J. D. Mikkelsen, N. Mrosovsky, Cellular colocalization of Fos and neuropeptide Y in the intergeniculate leaflet after nonphotic phase-shifting events. *Brain Res* **698**, 137–45 (1995).
455. B. Rusak, J. H. Meijer, M. E. Harrington, Hamster circadian rhythms are phase-shifted by electrical stimulation of the geniculo-hypothalamic tract. *Brain Res* **493**, 283–91 (1989).
456. H. E. Albers, C. F. Ferris, Neuropeptide Y: role in light-dark cycle entrainment of hamster circadian rhythms. *Neurosci Lett* **50**, 163–8 (1984).
457. M. E. Harrington, K. M. Schak, Neuropeptide Y phase advances the in vitro hamster circadian clock during the subjective day with no effect on phase during the subjective night. *Can J Physiol Pharmacol* **78**, 87–92 (2000).
458. L. Vidal, N. Lugo, Changes in neuropeptide Y immunoreactivity and transcript levels in circadian system structures of the diurnal rodent, the thirteen-lined ground squirrel. *Brain Res* **1125**, 77–84 (2006).
459. C. F. Gillespie, E. M. Mintz, C. L. Marvel, K. L. Huhman, H. E. Albers, GABA(A) and GABA(B) agonists and antagonists alter the phase-shifting effects of light when microinjected into the suprachiasmatic region. *Brain Res* **759**, 181–9 (1997).

460. C. M. Novak, H. E. Albers, Novel phase-shifting effects of GABAA receptor activation in the suprachiasmatic nucleus of a diurnal rodent. *Am J Physiol Regul Integr Comp Physiol* **286**, R820-5 (2004).
461. C. M. Novak, H. E. Albers, Circadian phase alteration by GABA and light differs in diurnal and nocturnal rodents during the day. *Behavioral neuroscience* **118**, 498–504 (2004).
462. R. D. Smith, S. Inouye, F. W. Turek, Central administration of muscimol phase-shifts the mammalian circadian clock. *J Comp Physiol A* **164**, 805–14 (1989).
463. R. A. Prosser, J. D. Miller, H. C. Heller, A serotonin agonist phase-shifts the circadian clock in the suprachiasmatic nuclei in vitro. *Brain Res* **534**, 336–9 (1990).
464. S. Shibata, A. Tsuneyoshi, T. Hamada, K. Tominaga, S. Watanabe, Phase-resetting effect of 8-OH-DPAT, a serotonin1A receptor agonist, on the circadian rhythm of firing rate in the rat suprachiasmatic nuclei in vitro. *Brain Res* **582**, 353–6 (1992).
465. R. A. Prosser, R. R. Dean, D. M. Edgar, H. C. Heller, J. D. Miller, Serotonin and the mammalian circadian system: I. In vitro phase shifts by serotonergic agonists and antagonists. *J Biol Rhythms* **8**, 1–16 (1993).
466. D. M. Edgar, J. D. Miller, R. A. Prosser, R. R. Dean, W. C. Dement, Serotonin and the mammalian circadian system: II. Phase-shifting rat behavioral rhythms with serotonergic agonists. *J Biol Rhythms* **8**, 17–31 (1993).
467. E. L. Meyer-Bernstein, L. P. Morin, Differential serotonergic innervation of the suprachiasmatic nucleus and the intergeniculate leaflet and its role in circadian rhythm modulation. *J Neurosci* **16**, 2097–111 (1996).
468. R. E. Mistlberger, M. C. Antle, J. D. Glass, J. D. Miller, Behavioral and Serotonergic Regulation of Circadian Rhythms. *Biological Rhythm Research* **31**, 240–283 (2000).
469. T. W. Lovenberg, *et al.*, A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. *Neuron* **11**, 449–58 (1993).
470. R. A. Cutrera, M. Saboureau, P. Pévet, Phase-shifting effect of 8-OH-DPAT, a 5-HT1A/5-HT7 receptor agonist, on locomotor activity in golden hamster in constant darkness. *Neurosci Lett* **210**, 1–4 (1996).
471. K. Horikawa, *et al.*, Nonphotic entrainment by 5-HT1A/7 receptor agonists accompanied by reduced Per1 and Per2 mRNA levels in the suprachiasmatic nuclei. *J Neurosci* **20**, 5867–73 (2000).
472. K. Horikawa, S. Shibata, Phase-resetting response to (+)8-OH-DPAT, a serotonin 1A/7 receptor agonist, in the mouse in vivo. *Neurosci Lett* **368**, 130–4 (2004).
473. M. Cuesta, J. Mendoza, D. Clesse, P. Pévet, E. Challet, Serotonergic activation potentiates light resetting of the main circadian clock and alters clock gene expression in a diurnal rodent. *Exp Neurol* **210**, 501–13 (2008).
474. L. Poncet, L. Denoroy, M. Jouvet, Daily variations in in vivo tryptophan hydroxylation and in the contents of serotonin and 5-hydroxyindoleacetic acid in discrete brain areas of the rat. *J Neural Transm Gen Sect* **92**, 137–50 (1993).
475. R. J. Reiter, The melatonin rhythm: both a clock and a calendar. *Experientia* **49**, 654–64 (1993).
476. V. M. Cassone, The pineal gland influences rat circadian activity rhythms in constant light. *J Biol Rhythms* **7**, 27–40 (1992).

477. P. Pévet, The internal time-giver role of melatonin. A key for our health. *Rev Neurol (Paris)* **170**, 646–52 (2014).
478. S. M. Reppert, D. R. Weaver, S. A. Rivkees, E. G. Stopa, Putative melatonin receptors in a human biological clock. *Science* **242**, 78–81 (1988).
479. D. R. Weaver, S. A. Rivkees, S. M. Reppert, Localization and characterization of melatonin receptors in rodent brain by in vitro autoradiography. *J Neurosci* **9**, 2581–90 (1989).
480. J. Vaněček, A. Pavlík, H. Illnerová, Hypothalamic melatonin receptor sites revealed by autoradiography. *Brain Res* **435**, 359–62 (1987).
481. S. M. Reppert, D. R. Weaver, T. Ebisawa, Cloning and characterization of a mammalian melatonin receptor that mediates reproductive and circadian responses. *Neuron* **13**, 1177–85 (1994).
482. D. R. Weaver, S. M. Reppert, The Mel1a melatonin receptor gene is expressed in human suprachiasmatic nuclei. *Neuroreport* **8**, 109–12 (1996).
483. J. Redman, S. Armstrong, K. T. Ng, Free-running activity rhythms in the rat: entrainment by melatonin. *Science* **219**, 1089–91 (1983).
484. B. Pitrosky, R. Kirsch, A. Malan, E. Mocaer, P. Pévet, Organization of rat circadian rhythms during daily infusion of melatonin or S20098, a melatonin agonist. *Am J Physiol* **277**, R812–28 (1999).
485. H. A. Sloten, B. Pitrosky, P. Pévet, Influence of the mode of daily melatonin administration on entrainment of rat circadian rhythms. *J Biol Rhythms* **14**, 347–53 (1999).
486. S. Schuhler, B. Pitrosky, R. Kirsch, P. Pévet, Entrainment of locomotor activity rhythm in pinealectomized adult Syrian hamsters by daily melatonin infusion. *Behavioural brain research* **133**, 343–50 (2002).
487. M. U. Gillette, A. J. McArthur, Circadian actions of melatonin at the suprachiasmatic nucleus. *Behavioural brain research* **73**, 135–9 (1996).
488. A. J. McArthur, M. U. Gillette, R. A. Prosser, Melatonin directly resets the rat suprachiasmatic circadian clock in vitro. *Brain Res* **565**, 158–61 (1991).
489. a J. Lewy, S. Ahmed, J. M. Jackson, R. L. Sack, Melatonin shifts human circadian rhythms according to a phase-response curve. *Chronobiol Int* **9**, 380–392 (1992).
490. S. Benloucif, M. L. Dubocovich, Melatonin and light induce phase shifts of circadian activity rhythms in the C3H/HeN mouse. *J Biol Rhythms* **11**, 113–25 (1996).
491. B. Bothorel, *et al.*, In the rat, exogenous melatonin increases the amplitude of pineal melatonin secretion by a direct action on the circadian clock. *Eur J Neurosci* **16**, 1090–8 (2002).
492. S. M. Armstrong, Melatonin and circadian control in mammals. *Experientia* **45**, 932–8 (1989).
493. J. Stehle, J. Vanecek, L. Vollrath, Effects of melatonin on spontaneous electrical activity of neurons in rat suprachiasmatic nuclei: an in vitro iontophoretic study. *J Neural Transm* **78**, 173–7 (1989).
494. C. Liu, *et al.*, Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron* **19**, 91–102 (1997).
495. U. Redlin, G. R. Lynch, Effects of pinealectomy on SCN electrical firing rhythm in Djungarian hamsters. *Neurosci Lett* **236**, 67–70 (1997).

496. M. H. Hastings, G. E. Duffield, E. J. Smith, E. S. Maywood, F. J. Ebling, Entrainment of the circadian system of mammals by nonphotic cues. *Chronobiol Int* **15**, 425–45 (1998).
497. J. D. Mikkelsen, N. Vrang, N. Mrosovsky, Expression of Fos in the circadian system following nonphotic stimulation. *Brain Res Bull* **47**, 367–76 (1998).
498. J. Schaap, J. H. Meijer, Opposing effects of behavioural activity and light on neurons of the suprachiasmatic nucleus. *Eur J Neurosci* **13**, 1955–62 (2001).
499. R. E. Mistlberger, M. M. Holmes, Behavioral feedback regulation of circadian rhythm phase angle in light-dark entrained mice. *Am J Physiol Regul Integr Comp Physiol* **279**, R813-21 (2000).
500. E. Challet, P. Pévet, Interactions between photic and nonphotic stimuli to synchronize the master circadian clock in mammals. *Front Biosci* **8**, s246-57 (2003).
501. P. Yannielli, M. E. Harrington, Let there be “more” light: enhancement of light actions on the circadian system through non-photic pathways. *Prog Neurobiol* **74**, 59–76 (2004).
502. S. M. Biello, N. Mrosovsky, Blocking the phase-shifting effect of neuropeptide Y with light. *Proceedings. Biological sciences / The Royal Society* **259**, 179–87 (1995).
503. S. M. Biello, Enhanced photic phase shifting after treatment with antiserum to neuropeptide Y. *Brain Res* **673**, 25–9 (1995).
504. E. L. Meyer-Bernstein, L. P. Morin, Electrical stimulation of the median or dorsal raphe nuclei reduces light-induced FOS protein in the suprachiasmatic nucleus and causes circadian activity rhythm phase shifts. *Neuroscience* **92**, 267–79 (1999).
505. E. Challet, F. W. Turek, M. Laute, O. Van Reeth, Sleep deprivation decreases phase-shift responses of circadian rhythms to light in the mouse: role of serotonergic and metabolic signals. *Brain Res* **909**, 81–91 (2001).
506. M. A. Rea, J. D. Glass, C. S. Colwell, Serotonin modulates photic responses in the hamster suprachiasmatic nuclei. *J Neurosci* **14**, 3635–42 (1994).
507. E. T. Weber, R. L. Gannon, M. A. Rea, Local administration of serotonin agonists blocks light-induced phase advances of the circadian activity rhythm in the hamster. *J Biol Rhythms* **13**, 209–18 (1998).
508. G. E. Pickard, M. A. Rea, Serotonergic innervation of the hypothalamic suprachiasmatic nucleus and photic regulation of circadian rhythms. *Biology of the cell / under the auspices of the European Cell Biology Organization* **89**, 513–23 (1997).
509. L. P. Morin, Serotonin and the regulation of mammalian circadian rhythmicity. *Ann Med* **31**, 12–33 (1999).
510. S. W. Ying, B. Rusak, Effects of serotonergic agonists on firing rates of photically responsive cells in the hamster suprachiasmatic nucleus. *Brain Res* **651**, 37–46 (1994).
511. M. Kohler, A. Kalkowski, F. Wollnik, Species differences between hamsters and rats with regard to the putative role of serotonin in the circadian system. *Biol. Rhythm Res.* **31**, 340–354 (2000).
512. Y. Shigeyoshi, *et al.*, Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. *Cell* **91**, 1043–1053 (1997).
513. U. Albrecht, Z. S. Sun, G. Eichele, C. C. Lee, A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light. *Cell* **91**, 1055–64 (1997).

514. L. P. Shearman, M. J. Zylka, D. R. Weaver, L. F. Kolakowski, S. M. Reppert, Two period homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. *Neuron* **19**, 1261–9 (1997).
515. L. Yan, S. Takekida, Y. Shigeyoshi, H. Okamura, Per1 and Per2 gene expression in the rat suprachiasmatic nucleus: Circadian profile and the compartment-specific response to light. *Neuroscience* **94**, 141–150 (1999).
516. M. J. Zylka, L. P. Shearman, D. R. Weaver, S. M. Reppert, Three period homologs in mammals: differential light responses in the suprachiasmatic circadian clock and oscillating transcripts outside of brain. *Neuron* **20**, 1103–10 (1998).
517. E. Challet, V. J. Poirel, A. Malan, P. Pévet, Light exposure during daytime modulates expression of Per1 and Per2 clock genes in the suprachiasmatic nuclei of mice. *Journal of Neuroscience Research* **72**, 629–637 (2003).
518. C. Fukuhara, *et al.*, Neuropeptide Y rapidly reduces Period 1 and Period 2 mRNA levels in the hamster suprachiasmatic nucleus. *Neurosci Lett* **314**, 119–22 (2001).
519. E. S. Maywood, H. Okamura, M. H. Hastings, Opposing actions of neuropeptide Y and light on the expression of circadian clock genes in the mouse suprachiasmatic nuclei. *Eur J Neurosci* **15**, 216–20 (2002).
520. J. M. Brewer, P. C. Yannielli, M. E. Harrington, Neuropeptide Y differentially suppresses per1 and per2 mRNA induced by light in the suprachiasmatic nuclei of the golden hamster. *J Biol Rhythms* **17**, 28–39 (2002).
521. J. C. Ehlen, *et al.*, GABAA receptor activation suppresses Period 1 mRNA and Period 2 mRNA in the suprachiasmatic nucleus during the mid-subjective day. *Eur J Neurosci* **23**, 3328–36 (2006).
522. V. J. Poirel, *et al.*, Contrary to other non-photoc cues, acute melatonin injection does not induce immediate changes of clock gene mRNA expression in the rat suprachiasmatic nuclei. *Neuroscience* **120**, 745–55 (2003).
523. W. J. Schwartz, R. Lydic, M. C. Moore-Ede, In vivo metabolic activity of the suprachiasmatic nuclei: non-uniform intranuclear distribution of ¹⁴C-labeled deoxyglucose uptake. *Brain Res* **424**, 249–57 (1987).
524. P. Vivanco, M. A. Rol, J. A. Madrid, Two steady-entrainment phases and graded masking effects by light generate different circadian chronotypes in *Octodon degus*. *Chronobiol Int* **26**, 219–41 (2009).
525. R. M. Calisi, G. E. Bentley, Lab and field experiments: are they the same animal? *Horm Behav* **56**, 1–10 (2009).