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

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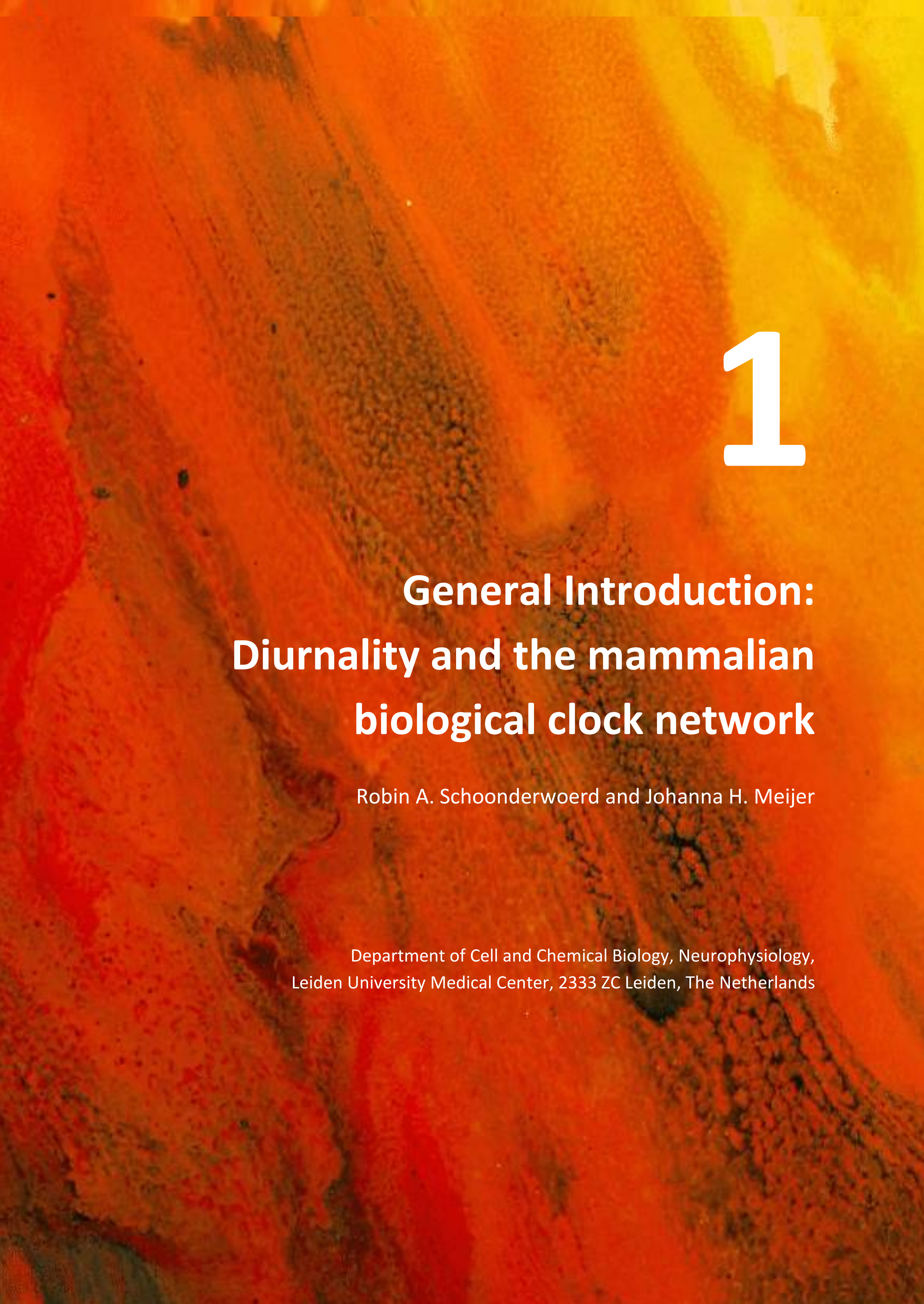

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General Introduction: Diurnality and the mammalian biological clock network

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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) ("circa-dies", 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.

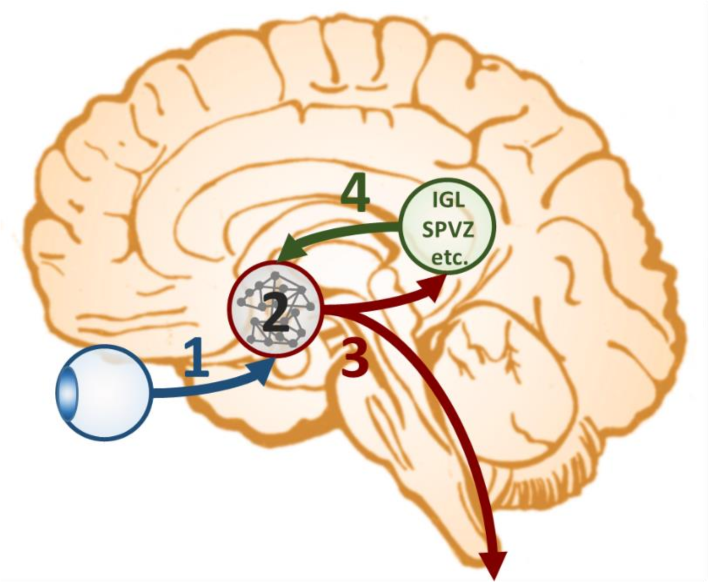

Figure 1: The four functional components of the biological clock. The biological clock requires (i) light input from the retina, (ii) a network structure within the suprachiasmatic nucleus (SCN) to maintain synchronous pacemaker activity, (iii) output pathways to the rest of the body and other brain 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 occurrs 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**
Acomys russatus	Golden spiny mouse*	Cohen *et al.* 2006, 2009 (62, 63)
Ammospermophilus leucurus	White-tailed antelope squirrel	Pohl *et al.* 1983 (64)
Arvicanthis ansorgei	Sudanian grass rat	Challet *et al.* 2002 (54)
Arvicanthis niloticus	Nile grass rat	Katona *et al.* 1997 (51)
Ctenomys aff. *knighti*	Catamarca tuco-tuco	Flôres *et al.* 2013 (65)
Eutamias sibiricus	Siberian chipmunk	Sato & Kawamura 1984 (66)
Funambulus palmarum	Palm squirrel	Navaneethakannan *et al.* 1986 (67)
Lemniscomys barbarus	Barbary striped grass mouse	Lahmam et al. 2008 (68)
Meriones unguiculatus	Mongolion gerbils#	Weinert *et al.* 2007 (69)
Octodon degus	Degu#	Lee & Labyak 1997 (48)
Psammomys obesus	Fat sand rat	Barak *et al.* 2013 (70)
Rhabdomys pumilio	Four-striped field mouse	Schumann *et al.* 2005 (71)
Spermophilus citellus	European ground squirrel	Hut *et al.* 1999 (56)
Spermophilus tridecemlineatus	Thirteen-lined ground squirrel	Meijer *et al.* 1989 (72)
Tamias striatus	Eastern chipmunk	Kramm *et al.* 1980 (73)
Tupaia belangeri	Tree shrew	Meijer *et al.* 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 (tau) and decrease activity phase (alpha/rho 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 arhythmicity 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.

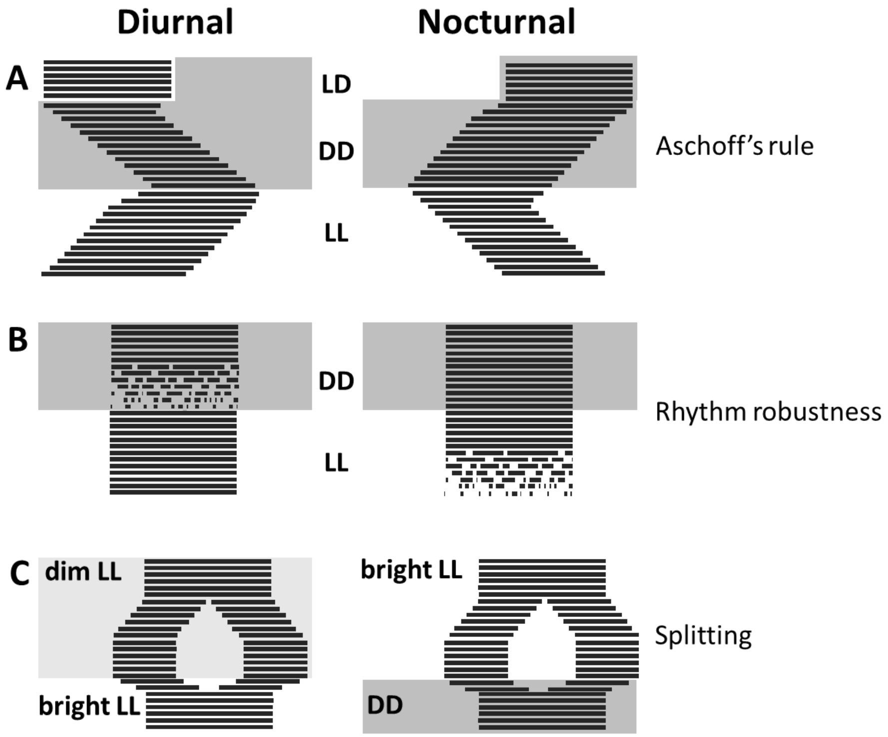

Figure 2: Diurnality in constant conditions. Diurnal and nocturnal species have different behavioural responses to constant conditions. This figure shows three distinct behaviours in constant conditions for diurnal and nocturnal species in schematically represented single plotted actograms. (A) According 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-photic stimuli on SCN rhythms are opposite to those of photic stimuli (109, 496–498). Non-photic 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-photic 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-photic and photic PRC are generally oppositely phased: light can increase PER most effectively when it is already low during the night and non-photic stimuli can decrease it when it is already high during the day (109). In contrast to other non-photic 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-photic 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 *et al.* 1996 (22)
	Glucocorticoid rhythm	≠	Halberg *et al.* 1959 (28)
	Melatonin rhythm	=	Reiter *et al.* 1985 (31)
Whole SCN	Metabolic activity rhythm	=	Schwartz *et al.* 1983 (93)
	Electrical activity rhythm	=	Sato & Kawamura 1984 (66)
Clock genes	Clock gene expression	=	Caldelas *et al.* 2003 (111)
Input	Light input pathway anatomy	=	Langel *et al.* 2015 (145)
	Cone percentage	≠	Hut *et al.* 2012 (39)
	Percentage light suppressed neurons	≠	Jiao *et al.* 1999 (206)
SCN network	Neuropeptide localization	=	Cohen *et al.* 2010 (271)
	VIP and GRP phase in constant darkness	≠	Dardente *et al.* 2004 (274)
	VIP and AVP phase relation	≠	Mammen *et al.* 2011 (159)
	Fos and neuropeptide colocalization	≠	Katona *et al.* 1998 (285)
	Light phase response curve	=	Lee & Labyak 1997 (48)
	Dead zone in phase response curve	≠	Beersma *et al.* 1999 (321)
	Dark pulse phase response curve	≠	Mendoza *et al.* 2007 (325)
	Period length and activity phase in constant light	≠	Aschoff *et al.* 1960 (4)
	Constant light intensities inducing splitting	≠	Meijer *et al.* 1990 (60)
	Rhythm robustness in constant conditions	≠	Refinetti *et al.* 2006 (332)
Output	SCN projections anatomy	=	Schwartz *et al.* 2011 (382)
	Fos expression in SPVZ	≠	Nunez *et al.* 1999 (390)

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

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