INTRODUCTION

Most life on this planet is subject to dramatic changes in environmental conditions brought about by the rotation of the Earth around its axis. With the succession of day and night parameters such as illumination, temperature, humidity, but also the presence or absence of food resources, potential mating partners, or predators may alter markedly. To adapt to these pervasive, but highly predictable variations in external challenges most organisms have evolved internal timekeeping systems—so called circadian clocks (from the Latin ‘circa diem’ meaning ‘about a day’)—to...
measure daytime and temporally coordinate physiology and behaviour.1,2

Circadian clocks affect a large spectrum of physiological outputs—from sleep-wake rhythms down to cell cycle regulation.2,3 Consequently, the disruption of circadian rhythms—as seen for example in shift workers or during jetlag—can have consequences for health and well-being. Many common chronic diseases of modern societies such as type-2 diabetes, major depression or cardiovascular disorders are promoted by chronodisruption, that is, the perturbation of internal clock function or of the alignment of these clocks with external time.4 Besides shift work, other chronodisruptive factors are sleep curtailment, high-energy diets or mistimed eating patterns, and nocturnal light pollution.5,6

2 | THE MOLECULAR CLOCK

In complex multicellular organisms such as mammals, molecular clocks are found in most, if not all, tissues and cells. They are based on a set of core clock genes, namely Brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (Bmal1, Arntl), Circadian locomotor output cycles kaput (Clock), Cryptochrome 1 and 2 (Cry1, Cry2) and Period 1, 2, 3 (Per1, Per2, Per3), and their protein products that encode time via interlocked transcriptional-translational feedback loops (TTFLs).7 In the core loop of the mammalian clock, the CLOCK:BMAL1 heterodimer binds to enhancer elements (E-boxes) regulating the transcription of Per, Cry and other clock-controlled genes (CCGs).8 PER:CRY dimers accumulate in the nucleus over the course of the day to inhibit the activity of the CLOCK:BMAL1 heterodimer and thereby regulate their own transcription.8 The degradation of the PER:CRY dimers during the second half of the day is controlled by the casein kinases CK1δ and CK1ε and determines the period length of the circadian clock.9 In a second TTFL, retinoic acid-related orphan receptors (Rora-γ) and reverse erythropoietic leukaemia (Rev-erba/β, Nr1d1/2) compete for binding to the retinoic acid-related orphan receptor response element (RORE) in the Bmal1 promoter sequence and are thereby stabilizing the core TTFL since RORs activate whereas REV-ERBs inhibit RORE-mediated gene transcription.9 In addition, another feedback loop acts via the regulation of destruction (D)-boxes, which were described in the promoter sequence of several clock genes.10 Nuclear factor, interleukin 3 regulated (NFIL3, E4BP4) is repressing, whereas D-site albumin promoter binding protein (DBP) is activating D-boxes.11 The diurnal activity of core clock genes as well as of CCGs is therefore controlled through binding of different protein regulators to E-boxes, D-boxes or ROREs.

To adapt these molecular oscillations to external time, the circadian TTFL can be reset by light as a main stimulus, but also other stimuli such as polyunsaturated fatty acids (PUFAs), carbon monoxide (CO) and nitric oxide (NO) were described to have resetting functions (Figure 1).12-15 Light stimulates the transcription of Per genes in the suprachiasmatic nucleus (SCN) resulting in entrainment of the circadian pacemaker to the day-night cycle.9 Per induction is mediated by cAMP response element-binding protein (CREB) and mitogen-activated protein kinase (MAPK) interaction with cAMP-response elements (CREs) in the promoter sequence of Per1 and Per2.9 PUFAs activate peroxisome proliferator-activated receptors (PPARs) which are then stimulating Bmal1 transcription.16 Additionally, PPARs have been reported to influence other clock components such as PER2 and REV-ERBα.17 Both, NO and CO signalling pathways, lead to a production of cyclic guanosine monophosphate which then activates protein kinase G to induce phase shifts.15

Cellular clocks organize biological functions through the regulation of extensive, but highly tissue-specific transcriptional programs. It has been estimated that more than 40% of all protein-coding genes are subject to circadian regulation in at least one tissue of the body.18 Chronodisruption may affect the clock system at different levels. Light pollution, for example, affects central clocks in the brain, but may additionally affect peripheral clocks indirectly while mistimed food intake is a dominant synchronizer (or Zeitgeber) for peripheral tissue clocks.19,20

3 | CLOCK HIERARCHY

The network structure of the mammalian circadian system is organized in a hierarchical fashion.21 At its top sits the SCN, a bilateral structure of densely packed neurons at the frontal ventromedial tip of the hypothalamus straddling the optic chiasm. The SCN receives light input directly from intrinsically light-sensitive retinal ganglion cells (ipRGCs) that express the photopigment melanopsin (OPN4). ipRGCs are most sensitive in the blue range of the visible spectrum (λmax = 480 nm) and capable of integrating light information over long periods of time.22 Through the retino-hypothalamic tract ipRGCs reset clocks in the SCN, thus directly entraining them to the external light-dark cycle. The endogenous oscillation of SCN clocks determines behavioural and physiological rhythms in the whole animal.23 Surgical lesioning of the SCN results in behavioural and molecular circadian arrhythmia,24 although short-period rhythms for some parameters may still be preserved.25 From the SCN, neuronal and humoral connections reach subordinate cellular clocks in the brain and throughout the periphery, aligning them with each other and with external time.

Neuronal tracing studies could show that the SCN projects predominantly to hypothalamic regions but it also
reaches some other brain regions such as, for example, the paraventricular nucleus of the thalamus (PVT) and the periaqueductal grey (Figure 2).26-30 SCN projections to the subparaventricular zone were reported to be involved in generating rest-activity rhythms.31 Projections from the SCN to the dorsomedial hypothalamus (DMH) and further to the locus coeruleus (LC) together with SCN projections to the lateral hypothalamus were described to regulate arousal and, thereby, sleep-wake behaviour.32,33 Direct projections from the SCN to the median preoptic nucleus (MPN) and the anteroventral paraventricular nucleus were described.34,35 Furthermore, the SCN innervates the paraventricular nucleus of the hypothalamus and is thereby regulating several hormonal axes as well as melatonin release, which in turn feeds back to the SCN.36,37 Incoming signals to the SCN originating from ipRGCs of the retina, that contain melanopsin, as well as metabolic stimuli integrate via the arcuate nucleus (ARC).38,39 The mechanisms of communication within the circadian clock network of the body are still poorly understood. Factors involved are autonomic activation, body temperature, endocrine factors such as melatonin or glucocorticoids (GCs), but also behavioural functions such as the sleep-wake cycle or the timing of food intake.20

As mentioned above, other Zeitgebers than light have been described that are capable of affecting the circadian clock system, not all of which act through the SCN. The timed intake of food is a potent synchronizer of peripheral tissue circadian clocks while having little effect on the SCN itself.40 Under extreme conditions, such as rest phase restricted feeding, this may lead to a complete uncoupling of central and peripheral clocks. It is believed that such internal chronodisruption may be one of the underlying reasons for the high prevalence of metabolic disorders in night shift workers.41 On the other hand, recent work on rodents with disabled SCN function suggests that light may adjust clock gene transcription in peripheral tissues independent of SCN function.42-44 The pathway of such peripheral photic resetting remains largely unclear, but direct autonomic

**FIGURE 1** Regulation of the molecular clock. On the molecular level the transcription of the core clock genes and clock-controlled genes (CCGs) is influenced by different promotor elements such as E-boxes, D-boxes and retinoic acid-related orphan receptor response element (RORE). The CLOCK:BMAL1 heterodimer regulates the transcription of Per, Cry, ROR, Rev-erb and other (CCGs) by E-box binding. ROR and REV-ERB compete for RORE binding in the promotor of CCGs as well as in the Bmal1 promotor and thereby either activate or inhibit transcription. A similar regulation takes place through DBP and NFIL3 competition for D-box binding in the promotor sequence of several CCGs as well as in the Per genes. While DBP is activating D-boxes, NFIL3 has an inhibitory effect. Several stimuli can reset the molecular clockwork such as polyunsaturated fatty acids (PUFAs) stimulating Bmal1 via PPARs, light stimulating Per gene transcription, or nitric oxide (NO) and carbon monoxide (CO) leading to an activation of the cyclic guanosine monophosphate (cGMP) — protein kinase G (PKG) signalling. PPAR, peroxisome proliferator-activated receptor
activation or behavioural responses to external lighting conditions may play a role.

Considering the complexity of the circadian clock network with its millions of cellular timekeepers, the interaction of different oscillators in the coordination of overt circadian rhythms in behaviour and physiology and the temporal harmonization of different rhythms across the body are important aspects of circadian timekeeping. The SCN is known to communicate with extra-SCN central nervous system (CNS) oscillators as well as with peripheral clocks.

**FIGURE 2** Suprachiasmatic nucleus (SCN) projections and incoming signals. Projections from the SCN mainly reach hypothalamic brain regions but also parts of the thalamus and midbrain (blue arrows). Incoming signals from intrinsically light-sensitive retinal ganglion cells (ipRGCs), the hormonal axes, melatonin, as well as metabolic stimuli are represented by orange arrows. ARC, arcuate nucleus; AVPV, anteroventral paraventricular nucleus; DMH, dorsomedial nucleus of the hypothalamus; LC, locus coeruleus; LH, lateral hypothalamus; MPN, median preoptic nucleus; PAG, periaqueductal grey; PVN, paraventricular nucleus; PVT, paraventricular nucleus of the thalamus; SCN, suprachiasmatic nucleus; sPVZ, subparaventricular zone; VLPO, ventrolateral preoptic nucleus.

**FIGURE 3** Clock network communication. The suprachiasmatic nucleus (SCN) synchronizes extra-SCN central nervous system (CNS) oscillators and peripheral tissue clocks. Extra-SCN CNS clocks, mostly dependent from SCN signals, regulate neuronal functions but also communicate with the periphery via neurohumoral and behavioural rhythms. Peripheral tissue clocks then influence physiological functions and rhythms. For details see text.
Extra-SCN CNS oscillator output signals modulate neuronal functions such as mood and cognition but also communicate with peripheral tissue oscillators via induction of behavioural rhythms, for example, food intake, or neurohumoral rhythms. Peripheral tissue clocks are then regulating physiological functions and rhythms such as energy metabolism.

Traditionally, the main power over temporal coordination had been assigned to the SCN and its entrainment by light. With the development of experimental tools to study clock function in specific tissues—for example, by tissue-specific gene targeting in mice—that view has been challenged. We know now that tissue clocks continue to measure time even when removed from the body and the main task of the SCN is the coordination of different tissue clocks with external time. Moreover, tissue-specific ablation of clock function has been used to identify physiological roles for specific tissue clocks. Ablation of clock function in liver cells, for example, impacts on glucose handling through regulation of glucose transporter expression in hepatocytes. Loss of clock function in pancreatic beta cells also impacts on glucose metabolism by inhibiting insulin secretion and, thus, postprandial glucose disposal. In the immune system, cell-type specific clocks have been implicated in cell migration and immune defences. Most of these studies have focused on tissues and cells of the periphery while arguably the most visible outputs of the circadian clock—from sleep to appetite and temperature regulation—are functions of the CNS. Emerging data start to reveal the complex coordination of circadian timekeeping in the brain.

4 | METHODOLOGICAL APPROACHES

Different methodological approaches have been used to investigate circadian oscillators and their function. These questions were mostly assessed by lesion studies and general or conditional genetic knockouts, but other techniques such as chemogenetics, optogenetics or clock rescue experiments in Bmal1 deficient mice were also used. All these approaches have their advantages and disadvantages or are used to focus on a certain strength, for example, specificity or efficiency.

Lesion studies have the advantage to compare, for example, task performance in the same mouse before and after the lesion and are widely used to investigate correlations between brain regions and behaviour. Lesions are achieved by the application of an electric current (electrolytic lesions), by neuron overstimulation with, for example, glutamate (excitotoxic lesions), or knife cuts. All these techniques have in common that they damage the whole tissue area and thereby also destroy its connectivity. Another option are tissue transplants which were used for studies of SCN function, but have so far not broadly been applied to the characterization of extra-SCN brain oscillators.

A conventional genetic knockout would leave the tissue intact, but there is the risk of developmental effects as, for example, described for Bmal1-deficient mice. Furthermore a global knockout is addressing gene function in the whole organism and not a certain tissue, which is achieved by conditional knockout. Viral approaches increase specificity, but often decrease efficiency compared to Cre/loxP-mediated conditional knockouts. The advantage of viral approaches is their potential for highly specific targeting of certain neuronal populations. Rescue experiments, for example, a rescue of Bmal1 expression in Bmal1-deficient mice—either virally or via a Cre mouse line—are another approach to investigate the function of circadian oscillators. Viral tracing studies have been used to investigate the connections between the SCN and other brain regions such as the paraventricular nucleus and the medial prefrontal cortex and can be advantageous for testing the connectivity between different brain oscillators.

Newer techniques such as chemo- or optogenetics allow for the functional characterization of specific neuronal populations in certain brain areas. While optogenetics allow a tight temporal control, intracranial transplants and repetitive stimulation are necessary to obtain effects in the circadian domain. Chemogenetics do not provide such a tight temporal control, but instead allow for long-time investigations with a single drug administration and without intracranial implants. It is, for example, possible to activate designer receptors exclusively activated by designer drugs (DREADDs) to directly manipulate circadian clock output.

Apart from the in-vivo studies there are several in-situ approaches to test clock function, for example, via gene or protein expression analyses. However, commercial antisera for several clock proteins are not always very specific, which might lead to problems in Western blots or immunohistochemical determinations. Explants from Per2::LUC mice were also used to study tissue circadian rhythms or to test for the effect of substances on tissue clock resetting. However, this method might not be ideal for neuronal population that cannot be isolated en bloc. Moreover, unwanted clock resetting during tissue preparation is possible.

5 | BRAIN CLOCKS OUTSIDE THE SCN

The retina was the first neuronal tissue outside the SCN to be shown to have endogenous, autonomous circadian rhythms of melatonin synthesis in vitro. Since then, by studying rhythms in expression of clock genes and electrical activity, a variety of regions all across the brain spanning from tel-
metencephalon were found to oscillate.\textsuperscript{45,67} Real-time bioluminescence recordings of clock gene reporters in different tissues allowed to investigate the sustainability of circadian oscillators when disconnected from the body. Of 27 different brain regions studied in mice by Abe et al, 14 showed rhythmicity beyond a single cycle. Most regions dampened fast indicating the dependency on pacemaker input.\textsuperscript{68} With the exception of very few extra-SCN brain regions, rhythmicity was lost after surgically or genetically ablating the SCN. These clocks were therefore called secondary or slave oscillators.\textsuperscript{45}

The only other region besides the SCN to fulfil all characteristics of a circadian pacemaker is the olfactory bulb (OB). Research from Granados-Fuentes et al showed that the rhythmicity of the OB is autonomous, entrainable and temperature compensated.\textsuperscript{69,70} Clock gene expression rhythms in the OB respond to light.\textsuperscript{71} Moreover, odour was able to induce cFOS rhythms in OB and the associated piriform cortex. These rhythms persisted in SCN-lesioned mice, but bulbectomy also abolished rhythmicity in the piriform cortex.\textsuperscript{72} Other cortical structures rhythmically express core clock components in a SCN-dependent manner in rats.\textsuperscript{73,74} Interestingly, restricted-feeding induces rhythms in the cerebral cortex of SCN-ablated mice.\textsuperscript{75} Cortical brain activity shows a diurnal pattern in humans and is speculated to be under GC-dependent circadian control.\textsuperscript{76,77} In the prefrontal cortex, stress induces \textit{Per}1 and \textit{cFos} mRNA expression independent of adrenalectomy in mice.\textsuperscript{78} Gonadal hormones may play a role in this context.\textsuperscript{79}

The hippocampus as a key structure of memory formation rhythmically expresses all core clock components.\textsuperscript{80,81} These rhythms persist in constant darkness (DD) and in organotypic slice cultures for several days.\textsuperscript{82} Interestingly, expression peak times correlate with the species' temporal niche.\textsuperscript{82,83} Melatonin can reset hippocampal clocks\textsuperscript{84} but pinealectomy does not markedly affect clock protein rhythmicity.\textsuperscript{85}

The amygdala is another subcortical structure of the limbic system, which also shows robust clock protein expression rhythms depending on a functional SCN.\textsuperscript{86} Amygdala clock rhythms are entrained by GCs,\textsuperscript{87,88} but adrenalectomy abolishes rhythms exclusively in the central nucleus but not the basolateral amygdala.\textsuperscript{86} Moreover, rhythms in the amygdala and the amygdala-associated bed nucleus of the stria terminalis (BNST) are also blunted after thyroid- and parathyroidectomy\textsuperscript{89}—but not after pinealectomy.\textsuperscript{85} Time-restricted feeding restores rhythms in the amygdala and BNST of adrenalectomized animals.\textsuperscript{80} Moreover, clocks in both tissues are sensitive to sex steroids.\textsuperscript{91}

The \textit{nucleus accumbens} (NAc) and caudate putamen make up most of the striatum, a region coordinating multiple functions of cognition and motivation. The ex-vivo rhythmicity of the NAc is disrupted after mood manipulation in mice\textsuperscript{92} and clock gene expression patterns are altered by a free-choice high-fat/high-sugar diet in rats.\textsuperscript{93} Natsubori et al showed that putamen slices exhibit robust rhythmicity despite a lack of dopaminergic input,\textsuperscript{94} which was previously hypothesized to be the major regulator of this brain clock.\textsuperscript{95} It therefore remains to be shown, how exactly these striatal brain oscillators are entrained.

It is still unclear how exactly the lateral habenula (LHb) of the epithalamus keeps time.\textsuperscript{96} An early study showed a circadian rhythm in firing rates in sync with the SCN and photic responsiveness of the habenula in rats.\textsuperscript{97} While another study found no increase in cFOS expression by light in mice.\textsuperscript{98} Sakhi et al proposed a more influential role of intrinsic signals compared to SCN-derived transmitters or visual information in the LHB.\textsuperscript{99} The LHb, thus, seems to be rather autonomous and self-sustained brain clock: ex-vivo oscillations persist independent of action potentials\textsuperscript{45} and even when prepared from SCN-ablated animals.\textsuperscript{100} Still, SCN input is needed to keep two distinct clocks within the habenula in sync.\textsuperscript{100} Again, obesogenic choice diets abolish rhythmicity in this region indicating a sensitivity to nutrient input.\textsuperscript{101}

Many hypothalamic extra-SCN oscillators are particularly sensitive to the metabolic state or food timing. Rhythms detected in the dorsomedial, the lateral and ventromedial hypothalamus (VMH) are weak unless animals are kept under time-restricted feeding conditions.\textsuperscript{102} The ARC is a critical region for the control of homeostasis. Despite robust rhythmicity in vitro,\textsuperscript{103} the ARC loses clock gene oscillations when food is restricted to the daytime in nocturnal animals.\textsuperscript{104} Genetic disruption of the SCN clock does not completely eliminate rhythmic dopamine release in the ARC indicating a semi-autonomous clock machinery.\textsuperscript{105} Nevertheless, cutting the connections between ARC and the SCN results in desynchronization of the former.\textsuperscript{106} Hypothalamic regions are important control centres of many rhythmic physiological functions. It is, therefore, not surprising that most areas show pronounced oscillations.\textsuperscript{68,79} Midbrain oscillators are less well characterized, and evidence of rhythmicity is often vague. For example, slice cultures of the \textit{substantia nigra} were deemed arrhythmic in one,\textsuperscript{68} but rhythmic even in SCN-lesioned rats in another study.\textsuperscript{94} Circadian gene expression is found in regions of the hindbrain and thalamus. For a thorough discussion see the recent review from Paul et al.\textsuperscript{67} Taken together, it becomes clear that circadian clocks are distributed throughout the brain. Most of these oscillators are strongly dependent on the SCN. However, some of these extra-SCN oscillators show a certain autonomy and appear sensitive to non-photic \textit{Zeitgebers} (Figure 4).

### 6. FUNCTIONAL STUDIES OF EXTRA-SCN OSCILLATORS

While, at least on the level of clock gene expression, 24-hour rhythms have been described across the whole brain...
(eg search for ‘ARNTL’ and select circadian times series data sets at https://gp3.mpg.de), for some of these regions, studies on the physiological significance of their clocks are just emerging. Considering the rising prevalence of neuropsychiatric disorders and their strong correlation with circadian rhythm alterations, there is a strong interest both from scientific and clinical sides. We here summarize some of the studies aimed at elucidating functional aspects of known extra-SCN brain clocks and oscillators (Table 1).

As mentioned above the OB houses a robust clock with pacemaker-like qualities. However, its functional significance is still not well known. It was suggested to regulate 24-hour rhythms in olfaction via vasoactive intestinal polypeptide signalling modulating OB outputs.\(^{107}\) Diurnal rhythms of α1-2-fucose in secondary olfactory neurons of the OB are dampened in clock gene mutant mice.\(^{108}\) OB-gated olfaction can enhance photic resetting of the SCN.\(^{109}\) The OB clock responds to feeding rhythms\(^{110}\) but OB ablation in rats does not affect food-anticipatory activity (FAA)\(^{111}\) nor running-wheel behaviour in general.\(^{70}\) In hamsters, however, olfactory bulbectomy lengthens free-running period in line with its modulatory input to SCN resetting.\(^{112}\)

Oscillators in the habenula were described in the rostral and caudal part\(^{113}\) as well as in the medial part of the LHB.\(^{114}\) LHB slices show a circadian rhythm in firing rates peaking in the late subjective light phase and depending on a functional molecular clock.\(^{99,100}\) Since presynaptic potentiation of ventral tegmental area (VTA)-projecting neurons of the LHB was reported in learned helplessness models of depression,\(^{115}\) a functional temporal influence of LHB rhythms on monoamine release and the reward system was suggested.\(^{113,116}\) Furthermore, a possible influence of the LHB clock on hedonic food intake was suggested because of absent day-night activity of PER2 in a mouse model of diet-induced obesity\(^{117}\) and a negative regulation of hedonic food intake by glutamatergic projections from the lateral hypothalamic area to the LHB.\(^{118}\) The LHB clock was further discussed in context of mood alternations and the regulation of sleep homeostasis.\(^{119,120}\) Clock gene expression levels in the LHB are affected by chronic mild stress.\(^{119}\) Sleep deprivation alters clock gene expression in the LHB and, interestingly, LHB-lesioned rats show altered sleep-wake rhythms with increased slow-wave sleep.\(^{120}\)

Clock-deficient Cry1/Cry2\(^{-/-}\) mice show depression-like behaviour associated with alterations in neuronal growth factor expression in the basolateral amygdala, suggesting that the clock is involved in amygdala functioning to modulate emotional states.\(^{121}\) Somatostatin mRNA in the amygdala is rhythmic and somatostatin-deficient mice lose circadian rhythms in anxiety-related behaviour indicating that the amygdala oscillator may be involved in the circadian modulation of anxiety.\(^{122}\)

The ARC is a main hub for the central integration of metabolic signals,\(^{26}\) whereby two neuronal populations are important: pro-opiomelanocortin neurons inhibit, whereas neuropeptide Y/agouti-related protein neurons increase appetite.\(^{123,124}\) Therefore, many studies investigated the effect of timing of food intake on the ARC oscillator. Clock gene

---

**FIGURE 4** Regulation of extra-SCN oscillators in the brain. Reported resetting signals, light, food, activity or hormones, are illustrated as symbols next to the described oscillator. DMH, dorsomedial nucleus of the hypothalamus; Lat., lateral; N., nucleus; SCN, suprachiasmatic nucleus; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area.
expression in the ARC responds to meal timing.\textsuperscript{104,125,126}
Rhythmic clock gene expression in neuroendocrine dopaminergic neurons of the ARC suggested that prolactin secretion might be under the control of the ARC oscillator.\textsuperscript{127}
Interestingly, rats with ablated SCN-ARC connections show arrhythmic GC levels, body temperature and locomotor activity in DD suggest a close interaction in SCN and ARC clocks in the regulation of these outputs.\textsuperscript{106} Guzmán-Ruiz et al reported that the balance of α-MSH release from the ARC together with arginine vasopressin neurons from the SCN is fundamental for the daily body temperature rhythm through projections to the MPN.\textsuperscript{128} Padilla et al investigated the effect

| Extra-SCN oscillator | Suggested function | Experimental evidence\textsuperscript{a} | Reference(s) |
|----------------------|-------------------|------------------------------------------|--------------|
| Olfactory bulb (OB)  | Olfaction          | Expression studies                       | 107          |
|                      | SCN photic resetting | Expression studies, Lesion studies\textsuperscript{a} | 109          |
| Lateral habenula (LHb) | Monoamine release, Reward | Electrophysiology, Expression studies, Electrophysiology | 116, 101,113 |
|                      | Food intake        | Expression studies, Lesion studies\textsuperscript{a} | 101,111,117  |
|                      | Mood               | Expression studies                       | 119          |
| Amygdala             | Sleep homeostasis  | Expression studies                       | 120          |
|                      | Emotion, anxiety   | Expression studies, Neuropeptide manipulation\textsuperscript{a} | 121,122      |
| Arcuate nucleus (ARC) | Prolactin secretion | Expression studies                       | 127          |
|                      | Body temperature   | Electrophysiology                        | 26           |
|                      | Sleep-wake cycle   | Neuropeptide manipulation\textsuperscript{a} | 129          |
| Dorsomedial hypothalamus (DMH) | Unknown (food anticipation discussed) | Lesion, Tissue clock manipulation\textsuperscript{a} | 55,102,130,131 |
| Ventromedial hypothalamus (VMH) | Food anticipation | Expression studies, Lesion studies\textsuperscript{a} | 137          |
|                      | Energy expenditure & thermogenesis | Tissue clock manipulation\textsuperscript{a} | 140          |
| Ventral tegmental area (VTA) | Reward | Expression studies, Clock gene manipulation | 141,142      |
|                      | Locomotor activity | Tissue clock manipulation\textsuperscript{a} | 144          |
|                      | Anxiety & depression | Tissue clock manipulation\textsuperscript{a} | 144          |
| Nucleus accumbens (NAc) | Stress response and anxiety | Clock gene manipulation, Expression studies | 148          |
|                      | Reward             | Clock gene manipulation, Expression studies | 150,151      |
|                      | Food anticipation  | Expression studies                       | 152,153      |
| Hippocampus          | Memory formation   | Clock gene manipulation                   | 154          |
|                      | Depression         | Expression studies                       | 158          |
| Cerebral cortex      | Mood               | Tissue clock manipulation\textsuperscript{a} | 57           |
|                      | Food anticipation  | Expression studies                       | 160          |
|                      | Jetlag regulation  | Expression studies                       | 161          |
| Cerebellum           | Unknown (food anticipation discussed) | Expression studies, Lesion studies\textsuperscript{a} | 162,163      |

\textsuperscript{a}In-vivo functional manipulation of tissue, tissue clock or tissue output.
of kisspeptin-expressing neurons in the ARC (Kiss1<sup>ARH</sup>) on locomotor activity, body temperature, sleep and food intake rhythms in female mice. Toxin-silencing of Kiss1<sup>ARH</sup> neurons leads to arrhythmic feeding patterns and increased body weight, but not food intake. Furthermore, daily activity is decreased in these mice, body temperature and locomotor activity rhythms become unstable along with alterations in the sleep-wake cycle. Data were gained from female mice but changes in locomotor activity rhythms and body weight were shown to be independent of ovarian estrogen.

The DMH was controversially discussed to be the side of the food-entrainable oscillator (FEO).<sup>55,102,130,131</sup> In particular, Fuller et al suggested a clock gene-based FEO within the DMH.<sup>132</sup> However, this study was partially refuted.<sup>133,134</sup> Retrograde tracing and DMH lesions suggest a neuronal network involving DMH-SCN interactions as likely source for FAA.<sup>135</sup> Studies with DMH-ablated mice suggest that clock gene expression in the DMH is sensitive to food intake but the DMH oscillator is not essential for FAA and temperature rhythms in mice.<sup>125</sup> Therefore, the function of the DMH oscillator remains to be shown.

Even if involved in synchronizing feeding rhythms, SCN- and VMH lesion experiments show that the VMH itself does not contain a self-sustained oscillator controlling feeding rhythms.<sup>136</sup> It may, however, be involved in FAA. Although VMH nucleus lesions do not abrogate FAA, they changed their development under restricted feeding conditions.<sup>137</sup> VMH lesions were also shown to influence temperature and locomotor activity rhythms in food-restricted rats.<sup>138</sup> By using mice with an ablation of <i>Sirtuin (Sirt1)</i> in stereodigenic factor 1 (SF1) neurons in the VMH it was shown that SIRT1 links nutritional signals to the circadian clock.<sup>139</sup> Targeted deletion of the essential clock gene, <i>Bmal1</i>, within these neurons alters circadian energy expenditure rhythms via brown adipose tissue thermogenesis.<sup>140</sup>

Disturbed clock gene expression in reward-related brain regions such as the VTA after chronic cocaine application suggests a role of the VTA clock in the regulation of reward pathways.<sup>141</sup> In <i>Per2</i> clock gene mutant mice, altered monoamine oxidase (Maoa) mRNA expression levels as well as reduced MAOA levels in the NAc is accompanied by elevated dopamine levels in the NAc.<sup>142</sup> Diurnal rhythms of tyrosine hydroxylase in the VTA are regulated by NAD+-dependent activity of SIRT1.<sup>143</sup> VTA specific clock knockdown leads to hyperactivity, reduced anxiety-related and increased depression-like behaviour.<sup>144</sup> A study with 6-hydroxydopamine-induced VTA lesions in rats suggests that the mesolimbic dopaminergic system is involved in regulating circadian drinking and locomotor activity rhythms.<sup>145</sup> While most neurons in the VTA are either dopaminergic or GABAergic, Luo et al described an additional non-dopaminergic, non-GABAergic neuronal population within the VTA. These cells selectively fire throughout the active phase and are most likely projecting to the hippocampus suggesting a second non-dopaminergic circadian function of the VTA oscillator.<sup>146</sup>

Unpredictable chronic mild stress models influence the rhythms of clock gene expression in the <i>nucleus accumbens</i> (NAc) in anhedonic rats.<sup>119,147</sup> Specific knock-down of <i>Per1</i> and <i>Per2</i> in the NAc by RNA interference increases anxiety-like behaviour.<sup>148</sup> Knock-down of another clock gene, <i>Rev-erba</i>, in the NAc modulates anxiety-related behaviour and sociability in female but not in male mice.<sup>149</sup> Diurnal rhythms in dopamine receptor D3 expression suggest an involvement in reward processing, especially since cocaine disrupts both NAc clock gene as D3 expression rhythms in this area.<sup>150,151</sup> Along this line, an involvement of NAc clocks in FAA and food entrainment was suggested.<sup>152,153</sup>

<i>Rev-erba</i> knockout mice show abnormal early long-term potentiation (LTP) in the hippocampus specifically during the subjective night.<sup>56</sup> Several clock gene mutant mice show abnormal LTP and deficits in learned behaviour.<sup>82,154</sup> Circadian reactivation of MAPK and cyclic adenosine monophosphate (cAMP) was suggested to influence long-term memory formation.<sup>155</sup> Phosphorylation of cAMP responsive element-binding protein (CREB) is rhythmic in hippocampal slices.<sup>156,157</sup>

Chronic unpredictable stress persistently changes clock protein levels in the hippocampus suggesting that the hippocampal oscillator might also have a role in depressive-like behaviour.<sup>158</sup> Finally, hippocampal neurons from <i>Per1</i> mutant mice have a depressed autophagic machinery which might increase vulnerability during cerebral ischaemia.<sup>159</sup>

A conditional knockout of <i>Bmal1</i> in neurons of the cerebral cortex was shown to influence behaviour and mood (depressive-like state) and reduced noradrenaline levels.<sup>57</sup> Protein kinase C gamma (PKCγ)-mediated stabilization of cerebral BMAL1 levels was shown to affect food anticipation<sup>160</sup> and depletion of noradrenergic innervation from the LC in <i>Eae2</i> mutant mice results in dampened cortical clock gene rhythms and alterations in photic entrainment under experimental light conditions.<sup>161</sup> Studies in mice with the hotspot mutation suggested cerebellar oscillators to be involved in food anticipation.<sup>162</sup> Targeted deletion of <i>Bmal1</i> in the granular layer of the cerebellum, however, had a strong influence on the cerebellar clock gene oscillations, but did not influence food anticipation.<sup>163</sup>

## Conclusion

In summary, despite the primary focus of the circadian field on deciphering the various functions of the SCN pacemaker for some decades, there is now a plethora of studies describing the involvement of different extra-SCN central oscillators in various physiological functions such as activity rhythms, appetite, memory formation and mood. Nevertheless, considering the broad impact of circadian disruption on cognitive and neuropsychiatric functions, there is...
a clear interest from both scientists and clinicians to further dissect the regulation of specific brain oscillators and their contribution to physiology and disease. Still, many brain clocks remain to be described. With new genetic tools such as virus-mediated gene editing or chemogenetics more specific targeting of neuronal subpopulations becomes possible in the circadian context. Such studies will without doubt help us to better understand circadian network regulation across the brain and potentially devise novel therapeutic avenues for the treatment of common brain disorders such as major depression or neurodegeneration.

ACKNOWLEDGEMENTS
This work was supported by grants from the German Research Foundation (DFG; OS353-7/1 and GRK-1957) to HO. HO is a Lichtenberg fellow of the Volkswagen Foundation.

CONFLICT OF INTEREST
The authors declare no competing interests.

ORCID
Henrik Oster https://orcid.org/0000-0002-1414-7068

REFERENCES
1. Pittendrigh CS. Temporal organization: reflections of a Darwinian clock-watcher. Annu Rev Rev. 1993;55:16-54.
2. Pilorz V, Helfrich-Förster C, Oster H. The role of the circadian clock system in physiology. Pfugers Arch. 2018;470(2):227-239.
3. Barclay JL, Tsang AH, Oster H. Interaction of central and peripheral clocks in physiological regulation. Prog Brain Res. 2012;199:163-181.
4. Levi F, Schibler U. Circadian rhythms: mechanisms and therapeutic implications. Annu Rev Pharmacol Toxicol. 2007;47:593-628.
5. Kolbe I, Oster H. Chronodisruption, metabolic homeostasis, and the regulation of inflammation in adipose tissues. Yale J Biol Med. 2019;92(2):317-325.
6. Navara KJ, Nelson RJ. The dark side of light at night: physiological, epidemiological, and ecological consequences. J Pineal Res. 2007;43(3):215-224.
7. Takahashi JS. Transcriptional architecture of the mammalian circadian clock. Nat Rev Genet. 2017;18(3):164-179.
8. Partch CL, Green CB, Takahashi JS. Molecular architecture of the mammalian circadian clock. Trends Cell Biol. 2014;24(2):90-99.
9. Buhr ED, Takahashi JS. Molecular components of the Mammalian circadian clock. Handb Exp Pharmacol. 2013;217:3-27.
10. Jolley CC, Ukai-Tadenuma M, Perrin D, Ueda HR. A mammalian circadian clock model incorporating daytime expression elements. Biophys J. 2014;107(6):1462-1473.
11. Ueda HR, Hayashi S, Chen W, et al. System-level identification of transcriptional circuits underlying mammalian circadian clocks. Nat Genet. 2005;37(2):187-192.
12. Husse J, Eichele G, Oster H. Synchronization of the mammalian circadian timing system: light can control peripheral clocks independently of the SCN clock: alternate routes of entrainment optimize the alignment of the body’s circadian clock network with external time. BioEssays News Rev Mol Cell Dev Biol. 2015;37(10):1119-1128.
13. Lavialle M, Champeil-Potokar G, Alessandri JM, et al. An (n-3) polyunsaturated fatty acid-deficient diet disturbs daily locomotor activity, melatonin rhythm, and striatal dopamine in Syrian hamsters. J Nutr. 2008;138(9):1719-1724.
14. Minegishi S, Sagami I, Negi S, Kano K, Kitagishi H. Circadian clock disruption by selective removal of endogenous carbon monoxide. Sci Rep. 2018;8(1):11996.
15. Artinian LR, Ding JM, Gillette MU. Carbon monoxide and nitric oxide: interacting messengers in muscarinic signaling to the brain’s circadian clock. Exp Neurol. 2001;171(2):293-300.
16. Greco JA, Oosterman JE, Belsham DD. Differential effects of omega-3 fatty acid docosahexaenoic acid and palmitate on the circadian transcriptional profile of clock genes in immortalized hypothalamic neurons. Am J Physiol Regul Integr Comp Physiol. 2014;307(8):R1049-R1060.
17. Chen L, Yang G. PPARs integrate the mammalian clock and energy metabolism. PPAR Res. 2014;2014:653017.
18. Zhang R, Lahens NF, Ballance HL, Hughes ME, Hogenessch JB. A circadian gene expression atlas in mammals: implications for biology and medicine. Proc Natl Acad Sci USA. 2014;111(45):16219-16224.
19. Tahara Y, Shibata S. Entrainment of the mouse circadian clock: Effects of stress, exercise, and nutrition. Free Radic Biol Med. 2018;119:129-138.
20. Astiz M, Heyde I, Oster H. Mechanisms of communication in the mammalian circadian timing system. Int J Mol Sci. 2019;20:343. https://doi.org/10.3390/ijms20020343.
21. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature. 2002;418(6901):935-941.
22. Hughes S, Jagnannath A, Hankins MW, Foster RG, Peirson SN. Photic regulation of clock systems. Methods Enzymol. 2015;552:125-143.
23. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. Science. 1990;247(4945):975-978.
24. Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc Natl Acad Sci USA. 1972;69(6):1583-1586.
25. Chiesa JJ, Cambras T, Carpentieri AR, Díez-Noguera A. Arhythmic rats after SCN lesions and constant light differ in short time scale regulation of locomotor activity. J Biol Rhythms. 2010;25(1):37-46.
26. Guzmán-Ruiz M, Saderi N, Cazanec-Márquez F, et al. The suprachiasmatic nucleus changes the daily activity of the arcuate nucleus α-MSH neurons in male rats. Endocrinology. 2014;155(2):525-535.
27. Morin LP, Goodless-Sanchez N, Smale L, Moore RY. Projections of the suprachiasmatic nuclei, subparaventricular zone and retrochiasmatic area in the golden hamster. Neuroscience. 1994;61(2):391-410.
28. Kriegsfeld LJ, Leak RK, Yackulic CB, LeSauter J, Silver R. Organization of suprachiasmatic nucleus projections in Syrian hamsters (Mesocricetus auratus): an anterograde and retrograde analysis. J Comp Neurol. 2004;468(3):361-379.
29. Novak CM, Harris JA, Smale L, Nunez AA. Suprachiasmatic nucleus projections to the paraventricular thalamic nucleus in nocturnal rats (Rattus norvegicus) and diurnal nile grass rats (Arviacanthis niloticus). Brain Res. 2000;874(2):147-157.
30. Hattar S, Kumar M, Park A, et al. Central projections of melanopsin-expressing retinal ganglion cells in the mouse. J Comp Neurol. 2006;497(3):326-349.
31. Abrahamson EE, Moore RY. Lesions of suprachiasmatic nucleus efferents selectively affect rest-activity rhythm. Mol Cell Endocrinol. 2006;252(1-2):46-56.
32. Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. Nat Neurosci. 2001;4(7):732-738.
33. Mahoney CE, Brewer JM, Bittman EM. Central control of circadian phase in arousal-promoting neurons. PLoS ONE. 2013;8(6):e67173.
34. Deurivelcher S, Burns J, Semba K. Indirect projections from the suprachiasmatic nucleus to the ventrolateral preoptic nucleus: a dual tract-tracing study in rat. Eur J Neurosci. 2002;16(7):1195-1213.
35. Watson RE, Langub MC, Engle MG, Maley BE. Estrogen-receptive neurons in the anteroventral periventricular nucleus are synaptic targets of the suprachiasmatic nucleus and peri-suprachiasmatic region. Brain Res. 1995;689(2):254-264.
36. Kalasek A, Teclamariam-Mesbah R, Pévet P. Efferent projections of the suprachiasmatic nucleus in the golden hamster (Mesocricetus auratus). J Comp Neurol. 1993;332(3):293-314.
37. Challet E. Minireview: entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. Endocrinology. 2007;148(12):5648-5655.
38. Baver SB, Pickard GE, Sollars PI, Pickard GE. Two types of melanopsin retinal ganglion cell differentially innervate the hypothalamic suprachiasmatic nucleus and the olivary pretectal nucleus. Eur J Neurosci. 2008;27(7):1763-1770.
39. Yi C-X, van der Vliet J, Dai J, Yin G, Ru L, Buijs RM. Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. Endocrinology. 2006;147(1):283-294.
40. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic region. Proc Natl Acad Sci USA. 2004;101(15):5339-5346.
41. Blum ID, Leliavski A, Tsang AH, Oster H, Eichele G. The circadian oscillator of the cerebral cortex: molecular, biochemical and behavioral effects of deleting the Arntl clock gene in cortical neurons. Cereb Cortex. 2018;28(2):644-657.
42. Blum ID, Zhu L, Moquin L, et al. A highly tunable dopaminergic oscillator generates ultradian rhythms of behavioral arousal. eLife. 2014;3:1-20.
43. Todd WD, Fenselau H, Wang J, et al. A hypothalamic circuit for the circadian control of aggression. Nat Neurosci. 2018;21(5):717-724.
44. McDearmon EL, Patel KN, Ko CH, et al. Dissecting the functions of the mammalian clock protein BMAL1 by tissue-specific rescue in mice. Science. 2006;314(5803):1304-1308.
45. Kondratov RV, Kondratova AA, Gorbacheva YV, Vykhanovets OV, Antoch MP. Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. Genes Dev. 2006;20(14):1864-1873.
46. Langhans W, Beneda B, Schütz G. Characterization of the multisyntropic neuronal control of the rat pineal gland using viral transneuronal tracing. Eur J Neurosci. 1998;10(1):128-145.
47. Teclamariam-Mesbah R, Ter Horst GJ, Postema F, Wortel J, Buijs RM. Anatomical demonstration of the suprachiasmatic nucleus-pinealine tract. J Comp Neurol. 1999;406(2):171-182.
48. Sylvester CM, Krout KE, Loewy AD. Suprachiasmatic nucleus projection to the medial prefrontal cortex: a viral transneuronal tracing study. Neuroscience. 2002;114(4):1071-1080.
49. Tsang AH, Astiz M, Leinweber B, Oster H. Rodent models for the analysis of tissue clock function in metabolic rhythms research. Front Endocrinol. 2017;8:27.
50. Lamia KA, Storch K-F, Weitz CJ. Physiological significance of a peripheral tissue circadian clock. Proc Natl Acad Sci USA. 2008;105(39):15172-15177.
51. Sadacca LA, Lamia KA, deLemos AS, Blum B, Weitz CJ. An intrinsic circadian clock of the pancreas is required for normal insulin release and glucose homeostasis in mice. Diabetologia. 2011;54(1):120-124.
52. Marcheva B, Ramsey KM, Buhr ED, et al. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinemia and diabetes. Nature. 2010;466(7306):627-631.
53. Scheiermann C, Gibbs J, Ince L, Loudon A. Clocking in to immunity. Nat Rev Immunol. 2018;18(7):423-437.
54. Druzd D, Matveeva O, Ince L, et al. Lymphocyte circadian clocks control lymph node trafficking and adaptive immune responses. Immunity. 2017;46(1):120-132.
55. Tahara Y, Hirao A, Moriya T, Kudo T, Shibata S. Effects of medial hypothalamic lesions on feeding-induced entrainment of locomotor activity and liver Per2 expression in Per2:luc mice. J Biol Rhythms. 2010;25(1):9-18.
56. Choi JE, Kim S, Lee J, Kim K, Kaang B-K. Circadian regulation by REV-ERβ mediated hipposcampal E-LEEP in a time-dependent manner. Exp Neurobiol. 2018;27(5):344-349.
57. Bering T, Carstensen MB, Wörtwein G, Weikop P, Rath MF. The Circadian oscillator of the cerebral cortex: molecular, biochemical and behavioral effects of deleting the Arntl clock gene in cortical neurons. Cereb Cortex. 2018;28(2):644-657.
58. Blum ID, Zhu L, Moquin L, et al. A highly tunable dopaminergic oscillator generates ultradian rhythms of behavioral arousal. eLife. 2014;3:1-20.
68. Abe M, Herzog ED, Yamazaki S, et al. Circadian rhythms in isolated brain regions. J Neurosci. 2002;22(1):350-356.

69. Granados-Fuentes D, Prolo LM, Abraham U, Herzog ED. The suprachiasmatic nucleus entrains, but does not sustain, circadian rhythmicity in the olfactory bulb. J Neurosci. 2004;24(3):615-619.

70. Granados-Fuentes D, Saxena MT, Prolo LM, Aton SJ, Herzog ED. Olfactory bulb neurons express functional, entrainable circadian rhythms. Eur J Neurosci. 2002;19(4):898-906.

71. Hamada T, Honma S, Honma K-I. Light responsiveness of clock genes, Per1 and Per2, in the olfactory bulb of mice. Biochem Biophys Res Commun. 2011;409(4):727-731.

72. Granados-Fuentes D, Tseng A, Herzog ED. A circadian clock in the olfactory bulb controls olfactory sensitivity. J Neurosci. 2006;26(47):12219-12225.

73. Rath MF, Rohde K, Fahrenkrug J, Möller M. Circadian clock components in the rat neocortex: daily dynamics, localization and regulation. Brain Struct Funct. 2013;218(2):551-562.

74. Rath MF, Rovsing L, Möller M. Circadian oscillators in the mouse brain: molecular clock components in the neocortex and cerebellar cortex. Cell Tissue Res. 2014;357(3):743-755.

75. Wakisaka H, Yoshinobu Y, Aida R, Moriya T, Akiyama M, Shibata S. Restricted-feeding-induced anticipatory activity rhythm is associated with a phase-shift of the expression of mPer1 and mPer2 mRNA in the cerebral cortex and hippocampus but not in the suprachiasmatic nucleus of mice. Eur J Neurosci. 2001;13(6):1190-1196.

76. Muto V, Jaspar M, Meyer C, et al. Local modulation of human brain rhythms by circadian rhythmicity and sleep debt. Science. 2016;353(6300):687-690.

77. Liston C, Cichon JM, Jeanneateau F, Jia Z, Chao MV, Gan W-B. Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. Nat Neurosci. 2013;16(6):698-705.

78. Chun LE, Woodruff ER, Morton S, Hinds LR, Spencer RL. Variations in phase and amplitude of rhythmic clock gene expression across prefrontal cortex, hippocampus, amygdala, and hypothalamic paraventricular and suprachiasmatic nuclei of male and female rats. J Biol Rhythms. 2015;30(5):417-436.

79. Chun LE, Christensen J, Woodruff ER, Morton SJ, Hinds LR, Spencer RL. Adrenal-dependent and -independent stress-induced Per1 mRNA in hypothalamic paraventricular nucleus and prefrontal cortex of male and female rats. Stress. 2018;21(1):69-83.

80. Jilg A, Lesny S, Peruzki N, et al. Temporal dynamics of mouse hippocampal clock gene expression support memory processing. Hippocampus. 2010;20(3):377-388.

81. Harbour VL, Weigl Y, Robinson B, Amir S. Phase differences in expression of circadian clock genes in the central nucleus of the amygdala, dentate gyrus, and suprachiasmatic nucleus in the rat. PLoS ONE. 2014;9(7):e103309.

82. Wang LM-C, Dragich JM, Kudo T, et al. Expression of the circadian clock gene Period2 in the hippocampus: possible implications for synaptic plasticity and learned behaviour. ASN Neuro. 2009;1(3):1-16.

83. Otalora BB, Hagenauer MH, Rol MA, Madrid JA, Lee TM. Period gene expression in the brain of a dual-phasing rodent, the Octodon degus. J Biol Rhythms. 2013;28(4):249-261.

84. Jilg A, Bechstein P, Saade A, et al. Melatonin modulates day-time-dependent synaptic plasticity and learning efficiency. J Pineal Res. 2019;66(3):e12553.

85. Amir S, Harbour VL, Robinson B. Pinealectomy does not affect diurnal PER2 expression in the rat limbic forebrain. Neurosci Lett. 2006;399(1-2):147-150.

86. Lamont EW, Robinson B, Stewart J, Amir S. The central and basolateral nuclei of the amygdala exhibit opposite diurnal rhythms of expression of the clock protein Period2. Proc Natl Acad Sci USA. 2005;102(11):4180-4184.

87. Pantazopoulos H, Dolutshad H, Davis FC. A fear-inducing odor alters PER2 and c-Fos expression in brain regions involved in fear memory. PLoS ONE. 2011;6(5):e20658.

88. Segall LA, Perrin JS, Walker C-D, Stewart J, Amir S. Glucocorticoid rhythms control the rhythm of expression of the clock protein, Period2, in the oval nucleus of the bed nucleus of the stria terminalis and central nucleus of the amygdala in rats. Neuroscience. 2006;140(3):753-757.

89. Amir S, Robinson B. Thyroidectomy alters the daily pattern of expression of the clock protein, PER2, in the oval nucleus of the bed nucleus of the stria terminalis and central nucleus of the amygdala in rats. Neurosci Lett. 2006;407(3):254-257.

90. Segall LA, Verwey M, Amir S. Timed restricted feeding restores the rhythms of expression of the clock protein, Period2, in the oval nucleus of the bed nucleus of the stria terminalis and central nucleus of the amygdala in adrenalectomized rats. Neuroscience. 2008;157(1):52-56.

91. Perrin JS, Segall LA, Harbour VL, Woodside B, Amir S. The expression of the clock protein PER2 in the limbic forebrain is modulated by the estrous cycle. Proc Natl Acad Sci USA. 2006;103(14):5591-5596.

92. Landgraf D, Long JE, Welsh DK. Depression-like behaviour in mice is associated with disrupted circadian rhythms in nucleus accumbens and periaqueductal grey. Eur J Neurosci. 2016;43(10):1309-1320.

93. Blanca-Velasquez AS, Unmehopa UA, Eggels L, et al. A free-choice high-fat high-sugar diet alters day-night Per2 gene expression in reward-related brain areas in rats. Front Endocrinol. 2018;9:154.

94. Natsubori A, Honma K, Honma S. Dual regulation of clock gene Per2 expression in discrete brain areas by the circadian pacemaker and methamphetamine-induced oscillator in rats. Eur J Neurosci. 2014;39(2):229-240.

95. Hood S, Cassidy P, Posset M-P, et al. Endogenous dopamine regulates the rhythm of expression of the clock protein PER2 in the rat dorsal striatum via daily activation of D2 dopamine receptors. J Neurosci. 2010;30(42):14046-14058.

96. Baño-Otálora B, Piggins HD. Contributions of the lateral habenula to circadian timekeeping. Pharmacol Biochem Behav. 2017;162:46-54.

97. Zhao H, Rusak B. Circadian firing-rate rhythms and light responses of rat habenular nucleus neurons in vivo and in vitro. Neuroscience. 2005;132(2):519-528.

98. Shuboni DD, Cramm SL, Yan L, et al. Acute effects of light on the activity rhythm is associated with a phase-shift of the expression of Per1 and Per2 mRNA in the cerebral cortex and hippocampus but not in the suprachiasmatic nucleus of mice. Eur J Neurosci. 2002;13(6):1190-1196.

99. Segall LA, Perrin JS, Walker C-D, Stewart J, Amir S. Timed restricted feeding restores rat hippocampal neurons express functional, entrainable circadian rhythms. J Neurosci. 2002;19(4):898-906.
101. Blanca-Velazquez A, la Fleur SE, Mendoza J. Effects of a free-choice high-fat high-sugar diet on brain PER2 and BMAL1 protein expression in mice. Appetite. 2017;117:263-269.

102. Mieda M, Williams SC, Richardson JA, Tanaka K, Yanagisawa M. The dorsomedial hypothalamic nucleus as a putative food-entrainable circadian pacemaker. Proc Natl Acad Sci USA. 2006;103(32):12150-12155.

103. Sellix MT, Egli M, Poletini MO, et al. Anatomical and functional characterization of clock gene expression in neuroendocrine dopaminergic neurons. Am J Physiol Regul Integr Comp Physiol. 2009;290(5):R1309-R1323.

104. Wang D, Opperhuizen A-L, Reznick J, et al. Effects of feeding time on daily rhythms of neuropeptide and clock gene expression in the rat hypothalamus. Brain Res. 2017;1671:93-101.

105. Miller J-EK, Granados-Fuentes D, Wang T, Marpegan L, Holy Buijs FN, Guzmán-Ruiz M, León-Mercado L, et al. Suprachiasmatic nucleus interaction with the arcuate nucleus: essential for organizing physiological rhythms. eneuro. 2017;4(2):1-14.

106. Miller J-EK, Granados-Fuentes D, Wang T, Marpegan L, Holy TE, Herzog ED. Vasoactive intestinal polypeptide mediates circadian rhythms in mammalian olfactory bulb and olfaction. J Neurosci. 2014;34(17):6040-6046.

107. Kriegsfeld LJ, Korets R, Silver R. Expression of the circadian oscillator in hypothalamic dorsomedial nucleus and the suprachiasmatic nucleus is critical for the expression of food-entrainable circadian rhythms and metabolism. Curr Biol. 2019;29(4):592-604.e4.

108. Davidson AJ, Aragona BJ, Werner RM, Schroeder E, Smith JC, Stephan FK. Food-anticipatory activity persists after olfactory bulb ablation in the rat. Physiol Behav. 2001;72(1-2):231-235.

109. Amir S, Cain S, Sullivan J, Robinson B, Stewart J. Olfactory stimulus enhancement light-induced phase shifts in free-running activity rhythms and Fos expression in the suprachiasmatic nucleus. Neurosci. 1999;92(4):1165-1170.

110. Albrecht A, Thiere M, Bergado-Acosta JR, Poranzke J, Müller B, Stork O. Circadian modulation of anxiety: a role for somatostatin in the amygdala. PLoS ONE. 2013;8(12):e84668.

111. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered diurnal patterns of amygdala gene expression. Amino Acids. 2015;47(7):1367-1377.

112. De Araujo LD, Roa SL, Bueno AC, et al. Restricted feeding schedules modulate in a different manner the expression of clock genes in rat hypothalamic nuclei. Front Neurosci. 2016;10:567.

113. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

114. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

115. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

116. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

117. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

118. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

119. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

120. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

121. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

122. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

123. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

124. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

125. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

126. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

127. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

128. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

129. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

130. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

131. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

132. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

133. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

134. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.

135. Christiansen SL, Bouzinova EV, Fahrenkrug J, Wiborg O. Altered expression pattern of clock genes in a rat model of depression. Int J Neuropsychopharmacol. 2016;19(11):1-12.
hypothalamus: one node in a hunger-arousal network. Eur J Neurosci. 2009;30(9):1730-1738.

138. Challet E, Pévet P, Lakhdar-Ghazal N, Malan A. Ventromedial nuclei of the hypothalamus are involved in the phase advance of temperature and activity rhythms in food-restricted rats fed during daytime. Brain Res Bull. 1997;43(2):209-218.

139. Orozco-Solis R, Ramadori G, Coppipi R, Sassone-Corsi P. SIRT1 relays nutritional inputs to the circadian clock through the Sirt1 neurons of the ventromedial hypothalamus. Endocrinology. 2015;156(6):2174-2184.

140. Orozco-Solis R, Aguilar-Arnal L, Murakami M, et al. The circadian clock in the ventromedial hypothalamus controls cyclic energy expenditure. Cell Metab. 2016;23(3):467-478.

141. Wang D-Q, Wang X-L, Wang C-Y, Wang Y, Li S-X, Liu K-Z. Molecular rhythms that correlate with depression-like behavior in mice. Brain Res. 2008;1211(1):1668-1684.

142. Hampp G, Ripperger JA, Houben T, et al. Regulation of monoamine oxidase A by circadian-clock components implies clock influence on mood. Curr Biol. 2008;18(9):678-683.

143. Logan RW, Parekh PK, Kaplan GN, et al. NAD+ cellular redox and SIRT1 regulate the diurnal rhythms of tyrosine hydroxylase and conditioned cocaine reward. Mol Psychiatry. 2018;24(11):1668-1684.

144. Mukherjee S, Coque L, Cao J-L, et al. Knockdown of Clock and Period 2 in the nucleus accumbens regulate anxiety-related behavior. Biol Psychiatry. 2010;68(6):503-511.

145. Isobe Y, Nishino H. Circadian rhythm of drinking and running-wheel activity in rats with 6-hydroxydopamine lesions of the ventral tegmental area. Brain Res. 2001;899(1-2):187-192.

146. Luo AH, Georges FE, Aston-Jones GS. Novel neurons in ventral tegmental area fire selectively during the active phase of the diurnal cycle. Eur J Neurosci. 2008;27(2):408-422.

147. Logan RW, Edgar N, Gillman AG, Hoffman D, Zhu X, McClung CA. Chronic stress induces brain region-specific alterations of molecular rhythms that correlate with depression-like behavior in mice. Biol Psychiatry. 2015;78(4):249-258.

148. Spencer S, Falcon E, Kumar J, et al. Circadian genes Period 1 and Period 2 in the nucleus accumbens regulate anxiety-related behavior. Eur J Neurosci. 2013;37(2):242-250.

149. Zhao C, Gammie SC. The circadian gene Nr1d1 in the mouse nucleus accumbens modulates sociability and anxiety-related behavior. Eur J Neurosci. 2018;48(3):1924-1943.

150. Ozburn AR, Falcon E, Twaddle A, et al. Direct regulation of diurnal Drd3 expression and cocaine reward by Npas2. Biol Psychiatry. 2015;77(5):425-433.

151. Falcon E, Ozburn A, Mukherjee S, Roybal K, McClung CA. Differential regulation of the period genes in striatal regions following cocaine exposure. PLoS ONE. 2013;8(6):e66438.

152. Angeles-Castellanos M, Salgado-Delgado R, Rodríguez K, Buijs RM, Escobar C. Expectancy for food or expectancy for chocolate reveals timing systems for metabolism and reward. Neuroscience. 2008;155(1):297-307.

153. Angeles-Castellanos M, Mendoza J, Escobar C. Restricted feeding schedules phase shift daily rhythms of c-Fos and protein Per1 immunoreactivity in corticolimbic regions in rats. Neuroscience. 2007;144(1):344-355.

154. Wardlaw SM, Phan TX, Saraf A, Chen X, Storm DR. Genetic disruption of the core circadian clock impairs hippocampus-dependent memory. Learn Mem. 2014;21(8):417-423.

155. Eckel-Mahan KL, Phan T, Han S, et al. Circadian oscillation of hippocampal MAPK activity and cAMP: implications for memory persistence. Nat Neurosci. 2008;11(9):1074-1082.

156. Rawashdeh O, Jilg A, Jedlicka P, et al. PERIOD1 coordinates hippocampal rhythms and memory processing with daytime. Hippocampus. 2014;24(6):712-723.

157. Rawashdeh O, Jilg A, Maronde E, Fahrenkrug J, Stehle JH. Period1 gates the circadian modulation of memory-relevant signaling in mouse hippocampus by regulating the nuclear shuttling of the CREB kinase p90RSK. J Neurochem. 2016;138(5):731-745.

158. Jiang W-G, Li S-X, Liu J-F, et al. Hippocampal CLOCK protein participates in the persistence of depressive-like behavior induced by chronic unpredictable stress. Psychopharmacology. 2013;227(1):79-92.

159. Rami A, Fekadu J, Rawashdeh O. The hippocampal autophagic machinery is depressed in the absence of the circadian clock protein PER1 that may lead to vulnerability during cerebral ischemia. Curr Neurovasc Res. 2017;14(3):207-214.

160. Zhang L, Abraham D, Lin S-T, et al. PKCy participates in food entrainment by regulating BMAL1. Proc Natl Acad Sci USA. 2012;109(50):20679-20684.

161. Warnecke M, Oster H, Revelli J-P, Alvarez-Bolado G, Eichele G. Abnormal development of the locus coeruleus in Ear2(Nr2f6)-deficient mice impairs the functionality of the forebrain clock and affects nociception. Genes Dev. 2005;19(5):614-625.

162. Mendoza J, Pévet P, Felder-Schmittbuhl M-P, Bailly Y, Challet E. The cerebellum harbors a circadian oscillator involved in food anticipation. J Neurosci. 2010;30(5):1894-1904.

163. Bering T, Carstensen A-M, Rath MF. Deleting the Arntl clock gene in the granular layer of the mouse cerebellum: impact on the molecular circadian clockwork. Acta Physiol. 2020;229:e13446. https://doi.org/10.1111/apha.13446