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Review

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Minutes, days and years: molecular interactions among different scales of biological timing

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Biological clocks are genetically encoded oscillators that allow organisms to keep track of their environment. Among them, the circadian system is a highly conserved timing structure that regulates several physiological, metabolic and behavioural functions with periods close to 24 h. Time is also crucial for everyday activities that involve conscious time estimation. Timing behaviour in the second-to-minutes range, known as interval timing, involves the interaction of cortico-striatal circuits. In this review, we summarize current findings on the neurobiological basis of the circadian system, both at the genetic and behavioural level, and also focus on its interactions with interval timing and seasonal rhythms, in order to construct a multi-level biological clock.

1. Biological timing as a multi-frequency clock

The ability to reliably sense, process and react to relevant characteristics of the physical environment is an attribute of life; indeed, when this faculty is compromised, cognitive and behavioural performance is severely impaired, because precise timing is ubiquitous and of great importance for physiology and behaviour. Biological timing includes diverse time-related processes that encompass several orders of magnitude [1,2], from microsecond processing to seasonal rhythms. Microsecond timing, for example, is crucial for sound localization, allowing animals to determine the interval it takes sound to travel from one ear to the other [3]. Millisecond timing is critical for motor control, speech generation and recognition, playing music and dancing [4] and has been proposed to depend upon a sensory-motor circuit comprising the cerebellum and the occipital, parietal and insular cortices [5]. In the seconds-to-minutes range, interval timing is involved in a number of fundamental behaviours such as foraging, decision-making and learning, via activation of cortico-striatal circuits [1]. Circadian timing refers to the 24 h range and governs a large array of physiological, metabolic and behavioural functions. In mammals, the circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [6]. Most—if not all—organisms exhibit daily and circadian rhythms with periods of *ca* 24 h, which also serve as the basis for seasonal-encoding mechanisms and might be related to lifespan-related processes. Finally, seasonal timing refers to rhythmic behaviour with a period which is close to the environmental annual cycle, such as reproductive or hibernation rhythms, controlled in mammals through a neuroendocrine circuit modulated by the pineal hormone melatonin [7]. Figure 1 summarizes the orders of magnitude implied in biological timing (from interval timing to seasonal rhythms), as well as the representative difference in relative amplitude, which indicates that high-frequency timing (i.e. in the seconds-to-minutes range) tends to exhibit a higher relative amplitude than low-frequency periods such as those exemplified by seasonal rhythms.

In particular, timing oscillators in the fast (seconds–minutes) and intermediate (circadian) frequencies might share some properties, including common steps in molecular pathways that lead to the neurochemical basis of such mechanisms. There is evidence suggesting that the circadian clock may influence the rate of the interval timer; however, these relationships have not been completely elucidated

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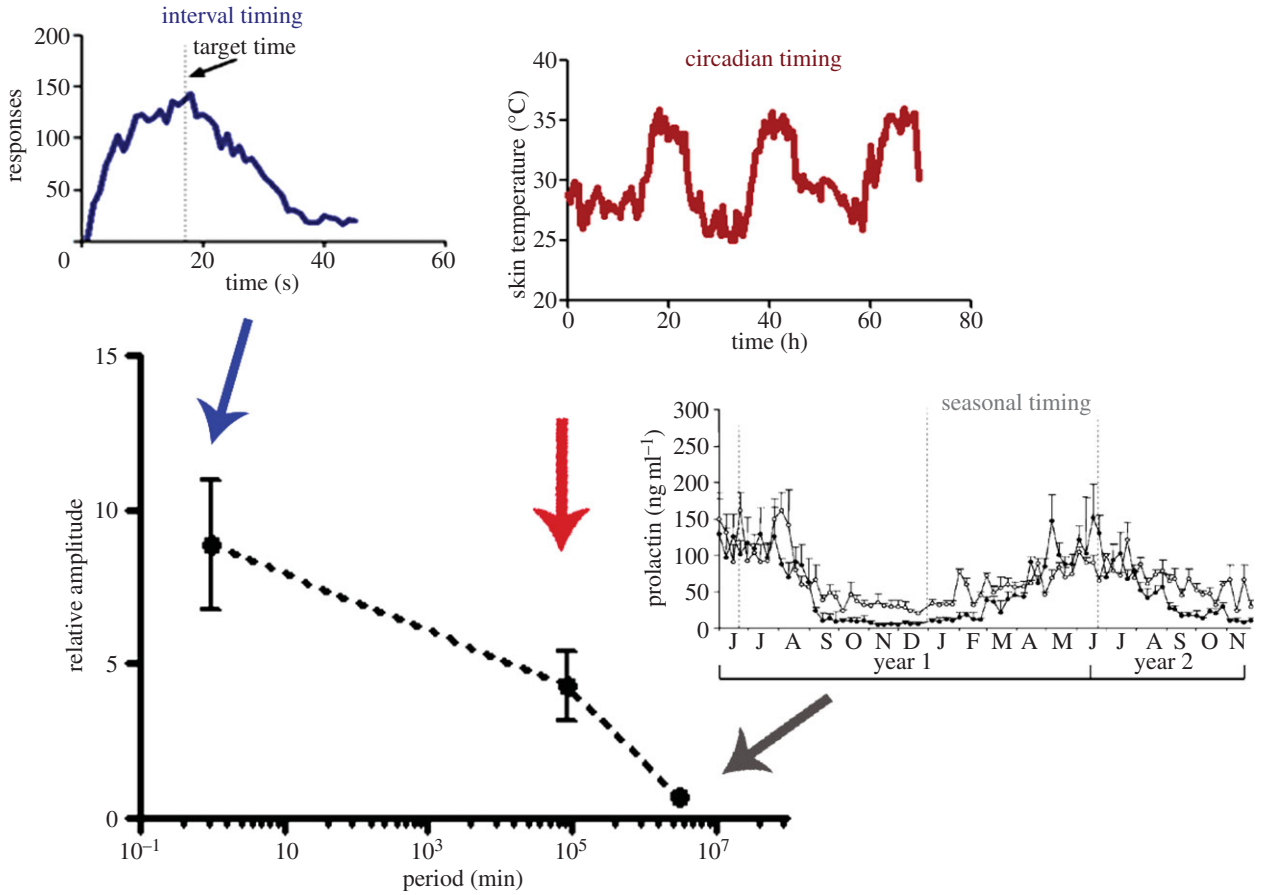

Figure 1. Relative amplitude of biological timing. Spectrum of biological timing phenomena, from interval timing to seasonal rhythms. The main graph shows the period of such timing mechanisms, spanning about seven orders of magnitude. When relative amplitude (calculated from representative data from the available literature by dividing the average amplitude values—considered as the difference between trough and peak values—by the minimal level of the variables) is compared, a negative correlation between period and amplitude of the oscillations/behavioural responses is found. Mean $\pm$ s.d. is shown, $n = 5-8$. Insets—described clockwise from the top—show representative data from interval timing, circadian timing and seasonal timing, respectively. Interval timing: response rate in mice trained to respond to a 17 s interval (data from authors' laboratory). Circadian timing: skin temperature from a 20-year-old female subject (data from authors' laboratory). Seasonal timing: plasma prolactin levels (ng ml^{-1}) throughout the year (adapted from [8]). (Online version in colour.)

at the behavioural or the molecular level. In this review, we focus on the general features of interval and, in particular, circadian timing, including genetic and molecular pathways underlying temporal coordination.

2. From very short (ultradian timing)...

Several biological mechanisms can be found in the ultradian temporal domain (less than 24 h). For example, the mammalian auditory system is a very precise sensory modality in terms of its temporal accuracy. Indeed, to spatially localize sounds coming from the left or the right, the binaural system can resolve time differences between the ears with microsecond precision. Discrimination of interaural time differences is performed by auditory midbrain neurons which are able to follow fast temporal modulations by 'coincidence-detecting' mechanisms [3]. Slightly longer temporal-control processes functioning in the milliseconds range, such as precise motor control, speech recognition and music perception, have been associated with cerebellar functioning [5]. In the seconds-to-minutes range, the conscious perception of time, known as interval timing, is crucial to learning, memory, decision-making and other cognitive tasks. As we shall discuss in §5, recent findings argue for the involvement of cortico-striatal circuits that are controlled by the dopaminergic modulation of oscillatory activity and lateral connectivity [9,10]. The ability to process time in the seconds-to-minutes range is impaired in patients with disorders that involve dopaminergic pathways, such as Parkinson's disease, Huntington's disease and schizophrenia [1].

A prominent temperature-compensated ultradian clock is the circa-hour (i.e. about 1 h period) that occurs from lower eukaryotes such as *Saccharomyces cerevisiae* [11] to mammals [12]. Recent experiments in cardiac cells reveal parallels and similarities with yeast in the dynamic and biochemical organization of ultradian redox oscillations [13]. The heartbeat mechanism has some unique features such as the activity of a dual pacemaker, e.g. a 'membrane clock' and a 'calcium clock', which might also be considered a model for molecular interactions among pacemakers [14]. Finally, fine-tuning endocrine information is coded by the circa-hour oscillation of hypothalamic–pituitary hormones, which is modulated along the oestrous or menstrual cycle, representing a complex temporal mechanism in which ultradian, circadian, infradian (i.e. several days) and even seasonal components control the neuroendocrine regulation of physiology and behaviour [12].

3. ...To very long (seasonal) timing

Organisms are affected by daily and seasonal variations of many physical factors of their environment. Seasonal timing, which refers to rhythms whose period correlates with the

annual environmental cycle, regulates several mechanisms, such as reproduction, diapause in insects, hibernation, fur colour changes and migration. In mammals, the pineal gland is a major component of the endocrine system that allows them to respond to the annual changes in photoperiod by adaptive alterations of their physiological state. This endocrine structure synthesizes and releases the hormone melatonin, which is secreted during the dark period of the light/dark cycle, independently of whether the animal is diurnally or nocturnally active, and the duration of the nocturnal melatonin peak is proportional to the length of the night. The brain is able to integrate photoperiodic information through these changes in duration of melatonin synthesis [7,15]. Melatonin modulates secretion of reproductive hormones by the anterior pituitary gland and also regulates the activity of the pars tuberalis [16].

It is interesting to consider that seasonal rhythmicity might be based, at least in part, on the activity of circadian pacemakers which are able to respond to photoperiod. In this sense, the SCN has also been called 'a clock for all seasons' regarding its ability to change circadian patterns throughout the year [17,18]. Again, intermodulation of diverse biological timing frequencies seems to be the key for temporal regulation.

4. Circadian timing: a day within the body

Circadian clocks generate self-sustaining, cell-autonomous oscillations with a time period of approximately 24 h. Features of a circadian clock in all organisms include its persistence under constant conditions, an oscillation that is temperature-compensated and its entrainment to external input. As the circadian system also modulates ultradian and infradian rhythms, in this review, we will emphasize the mechanisms of circadian clocks and rhythms.

(a) Genetics of circadian clocks

The molecular mechanism of the endogenous circadian clock comprises interlocking feedback loops involving cyclic gene products that control transcription by means of negative and positive regulation of 'clock' genes and proteins. The specific transcriptional/translational components differ between phylogenetic kingdoms [19]. In mammals, cell-autonomous circadian clocks are generated by a transcriptional autoregulatory feedback loop composed of the transcriptional activators CLOCK and BMAL1, and their target genes *Period* (*Per1* and *Per2*) and *Cryptochrome* (*Cry1* and *Cry2*). The latter (*Per* and *Cry*) are able to form a repressor complex that interacts with CLOCK/BMAL1 to inhibit their own transcription [20,21]. Post-translational events that modulate protein half-life and subcellular localization appear to contribute significantly to circadian oscillations. Several kinases and phosphatases regulate the speed, precision and function of the circadian clock [22,23]. Episodes of ubiquitination, acetylation/deacetylation and methylation also represent critical regulatory events that mediate circadian control [24–27]. Recent studies have implicated a number of microRNAs [28] and several RNA-binding protein complexes in the regulation of circadian polyadenylation, splicing, RNA stabilization and degradation [29]. Moreover, additional stabilizing feedback loops, including inhibition of *Bmal1* transcription by REV-ERBα [30], further contribute to the timing and robustness of the cycle. This cycling molecular framework can also control the transcription of other genes—called clock-controlled genes (CCGs)—by acting upon specific elements in their promoter regions, for example E-boxes (illustrated in figure 2). In addition, recent information suggests that non-transcriptional oscillator components appear to be conserved across kingdoms, revealing prominent post-translational contributions to timekeeping [31–34].

(b) Central and peripheral clocks

In multicellular organisms, for example mammals, there is a hierarchically structured circadian system [35]. At the top of this hierarchy is the SCN, which synchronizes subordinate organ and tissue clocks using electrical, neurochemical, endocrine and metabolic signalling pathways that impact the molecular mechanisms of cellular oscillators. The SCN consists of paired nuclei located in the ventral hypothalamus. In rats, each nucleus contains approximately 10 000 neurons, characterized by a small size and a high density [36]. Circadian SCN rhythmicity can be recorded at tisular level and is an emergent property of individual oscillators working together in synchrony [37]. Individual SCN cells have circadian rhythms in electrical activity, but with diverse period and phase [38,39]. Recent data highlight that, when isolated, SCN neurons exhibit a range of behaviours including damped or unstable circadian oscillations [40,41]. In this sense, several computational models have been proposed to understand the complex behaviours of SCN cells [42].

Shortly after the discovery of clock genes in mammals, it became evident that circadian clocks are present not only in SCN neurons but also in most, if not all, peripheral tissues. These peripheral clocks appear to have a molecular clockwork similar to the one described for the SCN. Thus, in both SCN cells and peripheral cells, the rhythm-generating molecular circuitry is based upon transcriptional/translational feedback loops involving essentially the same core clock components [43], although some variations are present, for example the neuronal PAS domain protein 2 (NPAS2) acting as a functional substitute for CLOCK in some brain areas [44,45]. Moreover, there are at least two circadian oscillators—a food-entrainable oscillator (FEO) and a methamphetamine (MAP)-entrainable oscillator (MASCO)—which are independent from the SCN and will be discussed in §4*c*.

(c) Synchronization of circadian clocks

The circadian clock is a self-sustained biological oscillator with a period close to 24 h in constant conditions. Circadian clocks in nature are normally exposed to a rhythmic environment, so that appropriate signals (*Zeitgebers*, from German Zeit, 'time'; geben, 'to give'), such as light, temperature or food, synchronize its oscillation [46]. In mammals, the most powerful synchronizer is the daily light/dark cycle. Light stimulates a group of photosensitive retinal ganglion cells that express the photopigment melanopsin [47] and project to the SCN through the retinohypothalamic tract. Glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP) are the primary neurotransmitters responsible for mediating the synchronizing properties of light, and act upon NMDA and AMPA/kainate receptors for glutamate and on the PACAP-specific receptor (PAC1). This leads to an increase of the intracellular concentrations of Ca^{2+}, which initiates a signal transduction cascade in SCN neurons that ultimately results in a phase shift of the circadian system [46,48–50].

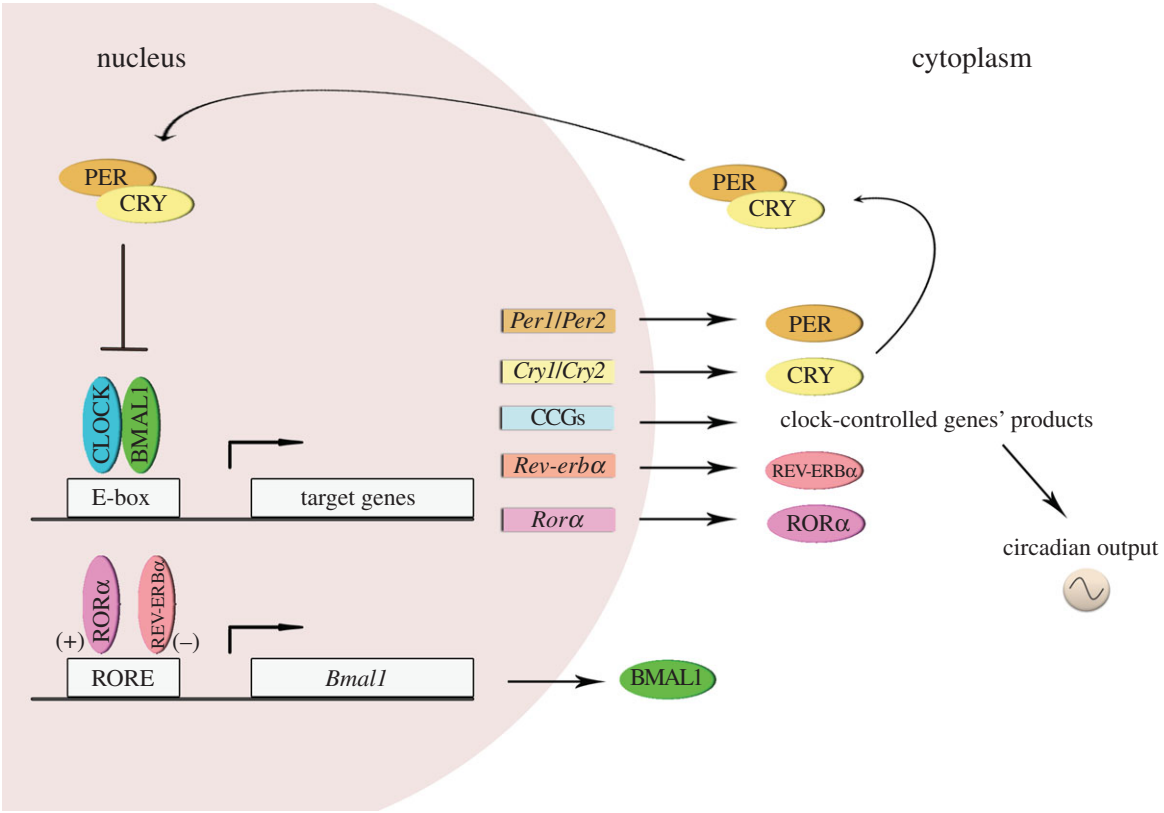

Figure 2. The molecular circadian clock in mammals. The molecular mechanisms of circadian rhythms can be illustrated by the transcription of the *Period* (*Per1* and *Per2*) and *Cryptochrome* (*Cry1* and *Cry2*) genes that are activated by heteromeric complexes containing CLOCK and BMAL1 proteins that act through the E-box regulatory sequences of their target genes. In turn, PER and CRY proteins inhibit BMAL1–CLOCK activity, and therefore, their own transcription. This core oscillation is augmented and stabilized by a secondary loop involving two orphan nuclear receptor proteins, REV-ERBα and RORα, which affect *Bmal1* expression. The result of these complex regulatory pathways is that the mRNA and protein levels of most circadian genes oscillate with approximately 24 h period. Importantly, the CLOCK–BMAL1 heterodimer regulates the transcription of many CCGs, which in turn influence a wide array of physiological functions external to the oscillatory mechanism. (Online version in colour.)

The circadian pacemaker varies in its temporal responsiveness to external stimuli. For example, in nocturnal rodents, exposure to light synchronizes circadian rhythms by inducing phase delays during the early night and phase advances during the late night, led by diverse signal transduction pathways which ultimately rely on the activation of transcription factors such as CREB and clock genes [51]. During the late night, when light induces phase advances of behavioural rhythms, photic stimulation specifically activates the guanylyl cyclase/cGMP/cGMP-dependent kinase (PKG) pathway [49,52]. Therefore, the accessibility of specific signalling pathways is fundamental for regulation of circadian timing.

Other entrainment cues, such as food intake, temperature, drugs or even social interaction, can reset circadian rhythms, eliciting phase shifts mainly during the subjective day (the resting period in rodents). Non-photic synchronization influences the SCN via two major input pathways, the geniculohypothalamic tract (GHT), and serotonergic (5HT) input from the dorsal raphe nucleus (DRN) and median raphe nucleus (MRN) [35]. However, two non-photically entrained circadian oscillators have been reported—a FEO and a MASCO—which are independent of the SCN [53,54]. When food availability is limited to a few hours during each day, mammals quickly alter daily rhythms of physiology and behaviour, such as locomotor activity, body temperature and corticosterone secretion, to correlate with the food availability rhythm [55]. Under these circumstances, a clear behavioural output is food-anticipatory activity (FAA), which implies an increase in locomotor activity that occurs before a daily timed meal. This food-entrainable oscillator is independent of the SCN and still displays clear circadian characteristics. One of its most important features is that FAA persists in the absence of food, suggesting that the FEO is able to generate a sustained free-running rhythm [53]. Similarly, the effects of MAP on circadian rhythms suggest the presence of an SCN-independent, MAP-sensitive circadian oscillator [54]. Nevertheless, the anatomical loci of these two oscillators are unknown (despite exhaustive searches for the FEO; [56]). It is worth noting that at least some features of circadian entrainment (such as non-photic synchronization induced by forced locomotion, feeding or neurochemical stimulation by metamphetamine and other agents) also depend upon reward-related mechanisms, including dopaminergic activation.

(d) Circadian clocks in metabolism, mood-related disorders and cognition

Food intake operates as a powerful *Zeitgeber* for entrainment of peripheral oscillators. Therefore, there is a tightly coupled relationship between metabolic state and the circadian clock, both at molecular and physiological levels [57]. Cycling of circadian components controls fundamental cellular and metabolic processes, including gluconeogenesis, oxidative phosphorylation, RNA processing and translation. Moreover,

Table 1. Genetic associations between circadian timing and cognitive, metabolic or mood-related disorders.

		gene	clinical association/alteration	reference
mood-related disorders	humans	*ARNTL*	bipolar disorder and seasonal affective/winter depression	[65–67]
		CLOCK	bipolar disorder and major depressive disorder	[68–71]
		CRY1	bipolar disorder and major depressive disorder	[69]
		CRY2	bipolar disorder and seasonal affective/winter depression	[72,73]
		NPAS2	bipolar disorder, major depressive disorder and seasonal affective/winter depression	[69,74]
		NR1D1	bipolar disorder	[75]
		PER2	depression and seasonal affective/winter depression	[67,76]
		PER3	bipolar disorder and schizoaffective disorder	[65,66,77]
		RORA	major depressive disorder	[76]
		RORB	bipolar disorder (pediatric)	[78]
	animals	*CLOCK*, *CLK*, *DBT* and *PER* mutants in *Drosophila*	lack of cocaine sensitization	[79]
		CLOCK-d19 mice	mania-like behaviour	[80]
		PER2-deficient mice	reduced depression- and anxiety-like behaviours	[45]
		RORB-deficient mice	reduced depression- and anxiety-like behaviours	[81]
metabolic disorders	humans	*RAI1*	obesity in Smith–Magenis syndrome	[82]
		CRY2 and melatonin receptor (*MTNR*) 1B	type-2 diabetes risk	[83]
	animals	*CLOCK*-d19 mice	obesity and metabolic syndrome similar to diabetes	[61]
		NPAS2-deficient mice	adaptability to food restriction	[44]
cognitive disorders	humans	*RAI1*	intellectual deficit	[82]
	animals	*PER* mutants in *Drosophila*	defective in long-term memory formation	[84]
		CRY1-CRY2 mutant mice	disrupted time–place learning	[85]

the SCN regulates circadian rhythms in leptin, plasma glucose, glucose tolerance, corticosteroids and cardiovascular function via neural and/or humoral signals to the white adipose tissue, liver, pancreas, adrenal cortex and heart [58]. Various hormones and metabolites that are generated by peripheral clocks feed back to the SCN, influencing specific brain functions [57,59]. Indeed, several of the core clock components function as 'redox sensors' which bind to nicotinamide adenine dinucleotide (NAD^+) and are modulated by the histone deacetylase SIRT1, both of which are influenced greatly by the nutrient levels in the organism [59].

Several lines of research suggest that alignment between central behavioural rhythms and feeding time is important in metabolic health. Animals fed a high-fat diet shift their pattern of food intake and consume nearly all of the excess calories at the incorrect circadian time, that is, during the rest period [60]. A similar misalignment of feeding between activity and rest is observed in Clock-mutant [61] and Npas2-knockout [43] mice, and a high-fat diet induces period lengthening in wild-type mice [60]. Similarly, mice fed with a high-fat diet exclusively during the rest period have accelerated weight gain as compared with animals fed during the correct circadian time [62]. Recent work indicates that the circadian clock in adipocytes affects the feeding rhythm of mice, which in turn exerts a profound influence on whole-body energy homoeostasis. Thus, adipocyte-specific deletion of a core circadian clock gene, *Arntl* (*Bmal1*), in mice shifts the timing of their feeding behaviour, resulting in obesity [63]. In humans, chronic circadian misalignment has been proposed to be the underlying cause for the adverse metabolic and cardiovascular health effects of shift work [64]. Information related to genetic associations between circadian timing and metabolic disorders is shown in table 1.

Animals with mutations or disruptions in the circadian machinery show changes in mood and behaviour. In mice, the Δ19 mutation in the *Clock* gene is accompanied by a spectrum of behavioural abnormalities including mania and hyperactivity [80]. Additionally, these animals as well as animals carrying mutations in the *Per* genes ($mPer1^{Brdm1}$ and $mPer2^{Brdm1}$ mutant mice) display altered sensitization to, and preference for, drugs of abuse such as cocaine [86,87] and alcohol [88,89]. *Clock* gene mutations appear to affect the dopaminergic system [45,80], among other neurochemical systems [89]. Also, mice deficient in the D2 receptor show aberrant light masking (light-induced suppression of locomotion) [90], and dopamine (DA) can regulate circadian expression of *Clock* genes [91,92]. These data suggest that defects in the clock system can alter DA synthesis and metabolism and might thereby contribute to depression-like symptoms. In humans, alterations in metabolic homoeostasis

Table 2. Genetic associations related to interval timing disorders.

	gene	clinical association/alteration	reference
humans	catechol-*O*-methyltransferase (*COMT* Val158Met polymorphism)	interval timing impaired in the suprasecond range and effect of reward magnitude	[118,119]
	dopamie receptor type 2 (*DRD2*/*ANKK1*-Taq1a polymorphism)	poorer performance with perceptual timing task and effect of reward magnitude	[118,119]
animals	*DAT*−/− mice	complete loss of temporal control. Hyperactivity and learning impairment; insensitive to psychostimulants	[120]
	D2R transgenic mice	impairment in timing accuracy and precision. Impairment in tasks that require working memory and behavioural flexibility	[115]

have been associated with mood disorders [93]. For example, together with metabolic syndrome, chronic shift work may favour the development of mood disorders [94], probably due to a misalignment of rhythms in body temperature, melatonin and sleep [95]. Conversely, individuals that suffer from mood disorders benefit from predictable daily routines including strictly followed bed- and mealtime [96]. These routines probably help to entrain and synchronize peripheral clocks in the body to maintain the integrity of the circadian system and physiology [97]. A typical mood disorder related to misalignment between environmental external and body internal rhythms is seasonal affective disorder (SAD), which is characterized by depressive symptoms that occur during the winter [98]. Phase delays in circadian secretion of cortisol and melatonin at specific times of the day have been observed in patients with either SAD or major depression, which further links the clock on a molecular level with these diseases [99]. Light therapy is an efficient method for the treatment of SAD [100], suggesting a connection between light-sensitive pathological mood states and light-sensitive circadian clocks. Disruptions in circadian rhythms have also been associated with bipolar disorder (BD) and major depressive disorder (MDD). Both BD and MDD involve deficits in reward processing and motivation, which are modulated by the circadian clock [101]. A number of polymorphisms in human circadian genes have been correlated with the incidence of BD and MDD (table 1). Moreover, antidepressants and mood stabilizers have been reported to entrain the circadian clock, which may affect drug efficacy, and therefore treatment viability [51]. Future studies will bring more light into the specific role of circadian clocks in the contribution to the pathophysiology of mood disorders, with the possibility of improving clinical treatments.

There is evidence that cognitive performance and learning may be influenced by circadian processes [102–104], and recent information reveals that regularly timed cognitive processes impact circadian rhythms [105], indicating a bidirectional interaction between cognitive performance and circadian processes. Furthermore, at least for some tasks in rodents, night-phase performance can never be equalled by light-phase performance regardless of the strength of entrainment to the schedule, which may have deep implications for shift work therapies [101]. In addition, desynchrony between internal and environmental time has been associated with impaired cognitive function in animals [106–108] and humans [109–112]. Although it is well established that cognitive abilities vary as a function of time of day, there is still a widespread view that the circadian clock has a singular role in cognition related to the control of the timing of sleep, and that the main factor for cognitive maintenance is the quality and duration of sleep. However, there is also evidence that indicates a circadian control of cognition beyond sleep timing, as revealed by forced desynchrony protocols [113,114].

5. Circadian clocks and interval timing: as time goes by

A fundamental component of cognition is the perception of the passage of time. As already stated, interval timing involves short-time estimation in the seconds-to-minutes range [1]. Striatal medium spiny neurons detect the coincident activity of specific beat patterns of cortical oscillations [9,10]. DA signalling has been shown to be involved in the regulation of interval timing speed, because DA receptor agonists or antagonists are able to shift the perception of the signal duration. In particular, striatal DA type 2 (D2) receptor plays an important role in the modulation of interval timing [115]. Activation of NMDA-type glutamate receptors is also critical for interval timing mechanisms [116,117]. In addition, recent studies of molecular genetics have demonstrated the importance of specific DA regulators on interval timing performance, for example the DRD2/ANKK1-Taq1a, which is a D2 receptor polymorphism associated with decreased D2 density in the striatum, and the genes regulating the catechol-*O*-methyltransferase (COMT) enzyme, which degrades catecholamines in the frontal cortex (table 2).

Current evidence suggests that the internal clock which mediates the perception of short durations is sensitive to temperature, attention, emotions, drug and diet manipulations [121,122], all of which can be modulated by the circadian system. Indeed, time-of-day effects have been observed for the timing of auditory and visual signals in the seconds-to-minutes range [123–126]. For example, several studies have shown that time judgements in humans covary with normal circadian rhythms [127,128]. Consistent with this finding, a circadian rhythm in time estimates was documented in control subjects, but it was found to be disrupted in shift workers [125]. Moreover, rats exhibit circadian variations in time perception similar to those that have been demonstrated in humans [129]. Furthermore, it was reported that sleep deprivation influences diurnal variation of time estimation in humans [130]. In *Drosophila melanogaster*,

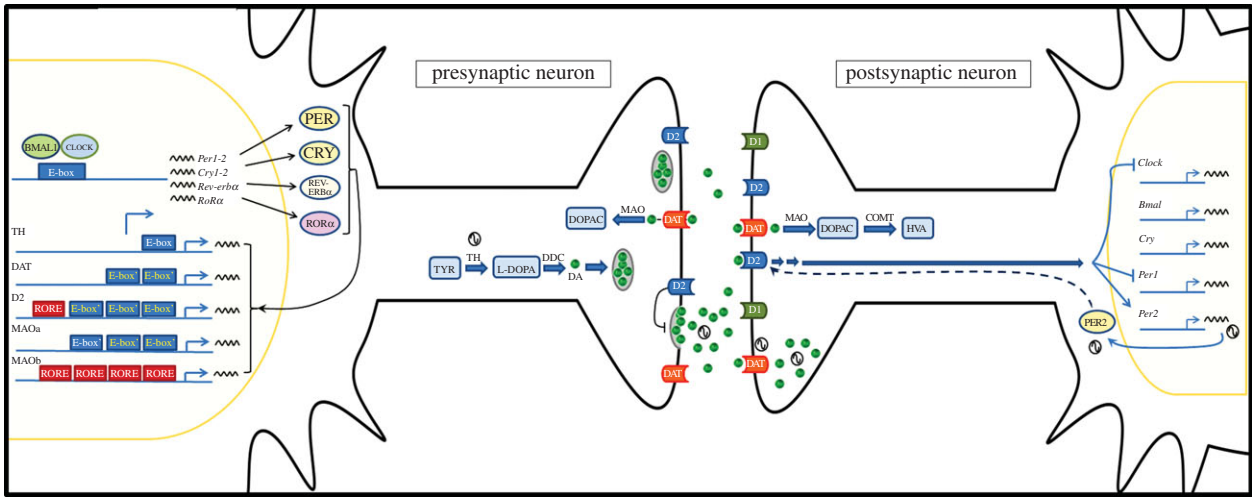

Figure 3. Molecular mechanisms for circadian modulation of interval timing. The circadian system control dopaminergic transmission at both presynaptic and postsynaptic levels. In presynaptic neurons—such as VTA or SN dopaminergic neurons—circadian clock proteins generate daily rhythms in the expression of components related to dopaminergic neurotransmission, mainly by acting as transcription factors through binding to E-boxes and ROR elements from promoter regions. Thus, the circadian control of dopaminergic enzymes could be involved either in rhythmic DA synthesis by TH, rhythmic DA release—under control of D2 autoreceptors—or rhythmic degradation mediated by DAT and MAO. On the other hand, in postsynaptic neurons—such as striatal medium spiny neurons—multiple levels of control by circadian components exist. There are daily rhythms in DAT expression, DA content and D2 receptor availability. In turn, dopaminergic function regulates the expression of clock genes through the activation of D2 receptors. COMT, Catechol-*O*-methyl transferase; D1, DA receptor type 1; D2, DA receptor type 2; DA, dopamine; DAT, DA transporter; DDC, DOPA decarboxylase; DOPAC, 3,4-dihydroxyphenylacetic acid; E-box', non-canonical e-box; HVA, homovanillic acid; MAO, monoamine oxidase; ROR, retinoid-related orphan receptor; RORE, ROR response element; SN, substantia nigra; TH, tyrosine hydroxylase; TYR, tyrosine; VTA, ventral tegmental area. (Online version in colour.)

timing of short intervals is disrupted in circadian mutants for each of the three allelic per mutations, per^s, per^l and per^o [131]. Recently, significant differences in the estimation of 24 s intervals at different times of day were reported in mice [132]. These differences were maintained under constant dark (DD) conditions, but impaired in mice under constant light (LL) conditions which abolish circadian rhythmicity. Moreover, short-time estimation in animals subjected to a 6 h advance of the light/dark cycle was transiently affected, indicating that temporal desynchronization of the circadian system is able to negatively affect time estimation. Taken together, these results suggest that short-time estimation is modulated by the circadian clock.

Figure 3 summarizes the principal molecular mechanisms supporting the various ways in which the circadian system interacts with interval timing. The main dopaminergic input to the striatum comes from the substantia nigra (SN) and the ventral tegmental area (VTA), and previous studies [133,134] have demonstrated the expression of circadian clock genes in these structures. The protein products of these clock genes act as transcription factors through binding to specific elements in promoter regions, such as E-boxes and RORE elements. These sequences have been found in the promoter region of components involved in dopaminergic metabolism, such as DA transporter (DAT), tyrosine hydroxylase (TH) and monoamine oxidase (MAO), suggesting that the expression of these components is under circadian regulation [45,135,136]. Some of them, like MAO, also exhibit diurnal rhythms in enzymatic activity [45]. Moreover, 24 h rhythms in DA levels and dopaminergic transmission were reported in both the striatum and nucleus accumbens [91,137]. In particular, the expression of DAT and TH showed a daily rhythm which was abolished in SCN-lesioned rats [138]. There is also evidence that indicate the regulation of DA receptors by circadian clock proteins in the striatum. In this sense, a 24 h rhythm in the expression of the DA D3 receptor was recently described, which is enhanced by RORα and inhibited by *Rev-Erbα* [139]. Moreover, a recent study [140] in humans suggested that a polymorphism in the PER2 protein correlates with striatal D2 receptor availability. Reciprocally, the blockade of D2 receptors blunted the rhythm of striatal PER2, and daily activation of D2 receptor restored and entrained the PER2 rhythm in a DA-depleted striatum in rats [87]. Moreover, quinpirole, a D2 receptor agonist, inhibited CLOCK and PER1 expression in the mouse striatum [141]. Taken together, these data suggest a circadian regulation of dopaminergic transmission in striatal circuits. This interaction at dopaminergic level could be in part responsible for the crosstalk between the circadian system and short-time estimation.

6. Constructing a multi-level biological clock

Several oscillators in the brain are involved in regulating timing behaviour in different temporal scales (figure 4). The interaction between circadian timing and other scales of biological timing—such as interval/circadian timing, or circadian/seasonal timing—may reflect an adaptive mechanism for living in a planet that rotates every 24 h. This 'multi-level' biological clock may contribute as a whole to human and animal behaviour.

We propose that at least some of the oscillators related to biological timing are linked by neurochemical/molecular common steps. Besides the well-known interaction between circadian and seasonal rhythmicity [17,142,143] in which the SCN was proposed as a 'clock for all seasons' by controlling annual or seasonal activity of the neuroendocrine axis, notably by modulating pineal melatonin secretion both

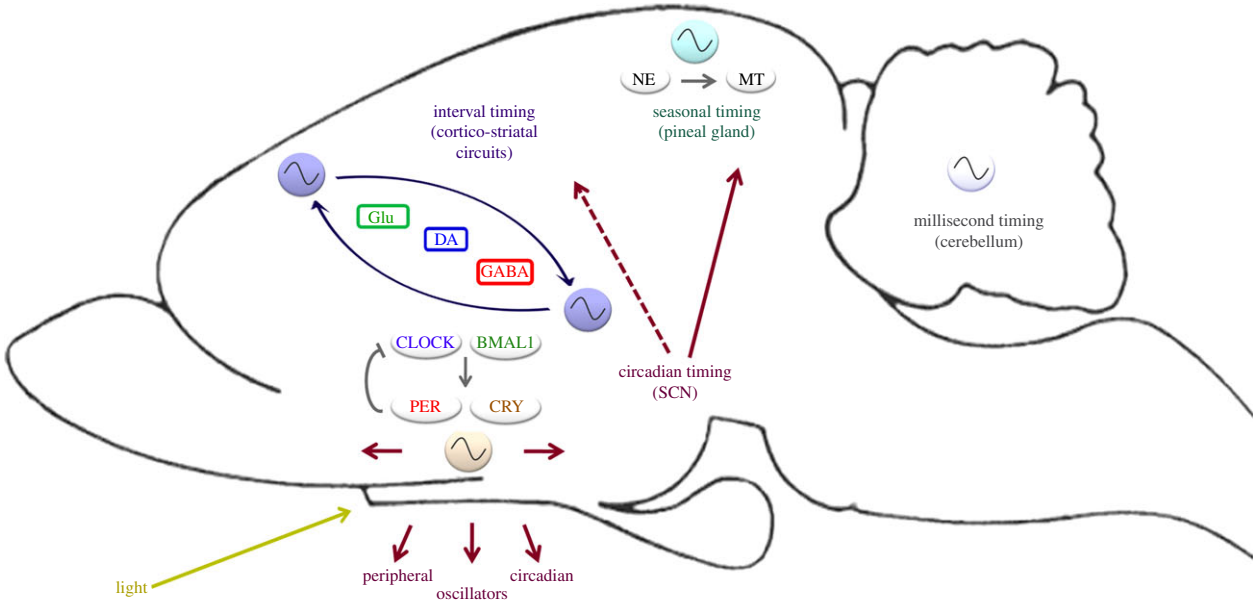

Figure 4. A network of oscillators regulates timing behaviour. The model represents mechanisms responsible for seasonal, circadian, interval and millisecond timing. In seasonal timing, the pineal gland allows mammals to respond to the annual changes in photoperiod by adaptive alterations of their physiological state. Melatonin, the major hormone produced by the pineal gland, displays daily and seasonal patterns of secretion which synchronize numerous physiological processes in photoperiodic species. In the range of approximately 24 h, circadian timing operates through a self-sustaining oscillator whose location in mammals is the SCN in the hypothalamus. The SCN controls several endocrine, metabolic and behavioural functions through peripheral oscillators. In the seconds-to-minutes range, interval timing depends upon cortico-striatal circuits. In the higher frequency range, millisecond timing has been proposed to depend upon a sensory-motor network that includes the cerebellum. These different oscillators can interact between themselves. Thus, release of melatonin by the pineal gland is mainly driven by the circadian clock, which controls the release of norepinephrine from the dense pineal sympathetic afferents. The circadian system could also modulate interval timing, perhaps through regulation of DA rhythms in the brain. BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; DA, dopamine; GABA, γ-aminobutyric acid; Glu, glutamate; MT, melatonin; NE, norepinephrine; PER, period. (Online version in colour.)

daily and throughout the year, here we suggest expanding this analogy to a 'multi-level biological clock' as a systemic approach to biological timing.

We have described in some detail the neurochemical and molecular bidirectional links between circadian and interval timers. Indeed, there is evidence for both time-of-day modulation of subjective time estimation processes and, conversely, for the regulation of the molecular circadian clock by neurochemical agents which are key actors of seconds-to-minutes timing. A common feature between these two systems is encoded by the reward-related mechanisms in the brain, which might function as powerful *Zeitgebers* of the circadian clock, and also provide a motivational framework underlying some of the main characteristics of interval timing. Pharmacological and molecular evidence suggests that dopaminergic homoeostasis might be regarded as a missing link between seconds, minutes and eventually days. A multi-level biological clock (for all seasons?) might be at the core of our timing capabilities and could fine-tune our appreciation of time.

In summary, temporal organization is a hallmark of life as an adaptation to environmental cycles and the ability to predict changes in the near future. Temporal misalignment may have severe consequences on physiology and behaviour which should be taken into account when designing work, school and health schedules. Current and future research on biological timing will certainly lead to an improvement in social temporal organization, leading to a better quality of life across the lifespan. Individuals, and societies, are the stuff of which time is made.

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