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Circadian rhythmicity and the community of clockworkers

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1 | INTRODUCTION: A 'SPECIAL' SPECIAL ISSUE

The Nobel Prize in Physiology or Medicine in 2017 was awarded for the study of the molecular/cellular basis of circadian rhythms in flies. The work was on flies is an example of a principle, repeated in subsequent decades, that simple model systems can uncover universal cellular and subcellular events. We briefly trace how this work opened new fields of research by making it possible to examine how circadian clocks work across many levels of analysis, from molecules, to cells, to tissues/glands and to whole organisms. The Nobel award provided an impetus for reflection: an opportunity to contemplate why research done in the early 1980s drew the Nobel committee's attention so many years later. What anteceded and followed the discovery of the cellular/molecular clock?

This issue of the *European Journal of Neuroscience* provides an overview of the field of circadian timing as a 'hub science' which reaches into psychology, medicine, cognition, sensory physiology, and decision-making. Both reviews and empirical papers are included. The papers fall into two broad categories, namely rhythms in simple and complex systems, and clocks in health, disruption and pathology (Table 1). The papers in this Special Issue highlight some of the contributions and contributors that have spread the word of the expanding impact of the field.

1.1 | Brief timeline of landmark discoveries in circadian timing

What was the status of understanding before the Nobel prize-winning work of Hall, Rosbash and Young (Nobelprize.org, 2019)? Early observations of circadian rhythms were regarded largely as curious phenomena. Salient features of these rhythms include persistence in constant environmental conditions with a period length of about 24 hr, resistance of period length to changes in temperature, and daily synchronization to environmental cues, most prominently to light. An example is the widely cited report of the daily movement of leaves in a plant kept in the dark (De Mairan, 1729). The puzzle was how did the plant detect the passage of days? What cues might be signalling the plant? In humans, some of the earliest studies of rhythms in heart rate and blood pressure

Abbreviations: AD, Alzheimer's disease; AhR, aryl hydrocarbon receptor; cAMP, cyclic adenosine monophosphate; CK, casein kinase; CREB, cAMP response element-binding protein; *Cry*, *cryptochrome*; CRY, CRYPTOCHROME; D2R, D2 dopamine receptor; DBT, double-time; EJN, European Journal of Neuroscience; FAA, food anticipation activity; GABA, gamma-aminobutyric acid; Glu, glutamate; HPA, hypothalamic–pituitary–adrenal (axis); ipRGC, intrinsically photosensitive retinal ganglion cells; LD, light–dark; MAPK, mitogen-activated protein kinases; PAS, Per-Arnt-Sim; PDF, pigment-dispersing factor; *Per*, *Period*; PER, PERIOD; PKA, protein kinase A; PKII, protein kinase II; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; TIM, TIMELESS; TST, total sleep time; TTFL, transcription translation feedback loop.

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TABLE 1 Contributions to the special issue on circadian rhythms

Section	Paper type	Invited Author(s)	Title
Circadian rhythms in simple systems	Review	Causton, Helen C.	Metabolic rhythms: A framework for coordinating cellular function
		Golden, Susan S.	Principles of rhythmicity emerging from cyanobacteria
		Loros, Jennifer J.	Principles of the animal molecular clock learned from Neurospora
Circadian rhythms in complex systems	Exp't	Gillette, Martha U.	Circadian rhythm of redox state regulates membrane excitability in hippo campal CA1 neurons
		Prosser, Rebecca A.	Copper in the suprachiasmatic circadian clock: A possible link between multi ple circadian oscillators
		Silver, Rae	Overexpression of striatal D2 receptors reduces motivation thereby decreasing food anticipatory activity
		Stengl, Monika	Circadian pacemaker neurons of the Madeira cockroach are inhibited and activ ated by GABAA and GABAB receptors
	Review	Evans, Jennifer A.	Circuit development in the master clock network of mammals
		Gamble, Karen L.	Circadian regulation of membrane physiology in neural oscillators throughout the brain
		Green, Carla B.	Periodicity, repression, and the molecular architecture of the mammalian circa dian clock
		Helfrich-Föerster, Charlotte	Flies as models for circadian clock adaptation to environmental challenges
		Honma, Sato	Development of the mammalian circadian clock
		Ko, Gladys Y.-P.	Circadian regulation in the retina: From molecules to network
		Mahoney, Megan M.	Modulation of circadian rhythms through estrogen receptor signaling
		Maywood, Elizabeth S.	Synchronization and maintenance of circadian timing in the mammalian clock work
		Mongrain, Valérie	Transcriptional control of synaptic components by the clock machinery
		Sehgal, Amita	Molecular and circuit mechanisms mediating circadian clock output in the Drosophila brain
		Sumová, Alena	Mystery of rhythmic signal emergence within the suprachiasmatic nuclei
Clocks in health and disruption	Exp't	Harrington, Mary E.	Recurring circadian disruption alters circadian clock sensitivity to resetting
		Martha Merrow	Strategies to decrease social jetlag: Reducing evening blue light advances sleep and melatonin
		Skene, Debra J.	Effect of acute total sleep deprivation on plasma melatonin, cortisol and metab olite rhythms in females
	Review	Boivin, Diane B.	Metabolic and cardiovascular consequences of shift work: The role of circa dian disruption and sleep disturbances
		Cirelli, Chiara	Sleep and synaptic down-selection
		Duncan, Marilyn J.	Interacting influences of aging and Alzheimer's disease on circadian rhythms
		Fu, Ying-Hui	The molecular genetics of human sleep
		González-Mariscal, Gabriela	Behavioral, neuroendocrine and physiological indicators of the circadian biolo gy of male and female rabbits
		Lyons, Lisa C.	Aging and the clock: Perspective from flies to humans
		McClung, Colleen A.	Mood-related central and peripheral clocks
		Meijer, Johanna H.	From clock to functional pacemaker
		Shirasu-Hiza, Mimi	Tired and stressed: Examining the need for sleep
		Simonneaux, Valérie	A Kiss to drive rhythms in reproduction
		Tischkau, Shelley A.	Mechanisms of circadian clock interactions with aryl hydrocarbon receptor signalling
		Vetter, Céline	Circadian disruption: What do we actually mean?
		Wirz-Justice, Anna	Perspectives in affective disorders: Clocks and sleep
		Yan, Lily - Smale	Circadian and photic modulation of daily rhythms in diurnal mammals
		Zee, Phyllis C.	Circadian disruption and human health: A bidirectional relationship

were done by Franz Halberg, who coined the term 'circadian' from the Latin for 'about a day'. A major leap from relative obscurity to attention emerged in the mid-twentieth century with the conceptualization of circadian rhythms as involving internal 'clocks' and 'oscillators' (reviewed by Schwartz & Daan, 2017). The clock/oscillator metaphor was extremely powerful and drew the attention of diverse researchers, as oscillator properties were the domain of many disciplines including mathematics, physics, statistics and engineering (reviewed by Pauls, Honma, Honma, & Silver, 2016). The notion of a clock/oscillator in the body also provoked a search for biological mechanisms of oscillators.

2 | CELLULAR CLOCKS

Evidence for a clock in the body came with the advent of mutation screening in *Drosophila melanogaster*. Ronald Konopka and Seymour Benzer discovered that mutations in a single functional gene, termed the *period* (*Per*) gene, produced either a short (19 hr) or long (28 hr) period rhythm, or arrhythmicity, in both population eclosion and in locomotor activity of individuals (Konopka & Benzer, 1971). This work in flies showed for the first time that a single gene mutation could alter a complex behaviour. In broad strokes, the Nobel Prize winners Jeff Hall, Michael Rosbash and Michael Young isolated the *Period* gene that encodes the protein called PERIOD (PER) (Bargiello, Jackson, & Young, 1984; Zehring et al., 1984). They showed that PER accumulates in cells during the night and degrades during the day (Siwicki, Eastman, Petersen, Rosbash, & Hall, 1988). This oscillation between accumulation and degradation of the protein controls daily biological rhythms within cells (Hardin, Hall, & Rosbash, 1990; Liu et al., 1992; Price et al., 1998; Vosshall, Price, Sehgal, Saez, & Young, 1994). We now know that this cellular clock involves two feedback loops and can be modulated by environmental signals (e.g. light and temperature) (see reviews by Helfrich-Forster, Bertolini, & Menegazzi, 2019; King & Sehgal, 2019). Unlike mammals, the molecular clock component *Cryptochrome* (encoding the protein called CRY) itself is light-sensitive, allowing these organisms to have very high sensitivity to light (Vinayak et al., 2013). At the tissue level, the invertebrate circadian clock was localized to the optic lobe through classic lesion and transplantation experiments in the cockroach (Page, 1982).

The conservation of a molecular clock was realized with the discovery of a great number of 'clock genes' and a very similar organization/mechanism among species (Pilorz, Helfrich-Forster, & Oster, 2018). Thus, a series of papers published in the 1990s described the novel Clock-Δ19 mutant (King et al., 1997; Vitaterna et al., 1994), cloning of *Bmal1* (Hogenesch et al., 1997) and the transcriptional control of CLOCK-BMAL1 activation of gene targets (Gekakis et al., 1998). The negative molecular clock components were next cloned, including *Drosophila Per* homologues (*Period* 1, 2, and 3) and the novel PER binding partner, CRYPTOCHROMEs (from *Cry1* and *Cry2* gene transcription) (Albrecht, Sun, Eichele, & Lee, 1997; van der Horst et al., 1999; Kume et al., 1999; Shearman, Zylka, Weaver, Kolakowski, & Reppert, 1997; Shigeyoshi et al., 1997; Vitaterna et al., 1999; Zylka et al., 1998). Since these seminal discoveries, this simple molecular clock has been expanded to include an accessory loop involving additional clock components, post-transcriptional regulators and structural dynamics. Figure 1 compares basic molecular clock components of flies and mammals (Lim, Christopher, Noguchi, & Golden, 2017). A review of these landmark discoveries and the current status of the mammalian molecular clock is presented in this Special Issue (Rosensweig & Green, 2019).

2.1 | Suprachiasmatic nucleus as the master clock

For circadian timing, a giant step to a 'Nobel-worthy' scientific research area was the localization of a 'master' circadian clock in the hypothalamic suprachiasmatic nucleus (SCN) (reviewed in Weaver, 1998). First, the retinohypothalamic tract (RHT) from retinal ganglion cells to the SCN was identified (Moore & Lenn, 1972). This pointed to a brain region (the SCN) that received photic input but was not a part of the classical visual system for pattern vision. Lesion studies showed that ablation of the SCN resulted in a loss of rhythmicity and an inability to synchronize (entrain) to the light–dark (LD) cycle, even though vision was not impaired (Moore & Eichler, 1972; Stephan & Zucker, 1972).

The SCN itself produces oscillations of electrical activity with a circadian period even when acutely dissociated in vitro (Green & Gillette, 1982), solidifying the clock concept. The work done in the decades following its initial discovery includes the demonstration that the clock tissue can be transplanted and that the transplanted tissue can restore rhythmicity to an arrhythmic host animal. The work was supported by the demonstration by immunochemistry that restoration occurs if the transplant includes SCN tissue, but not if the transplanted tissue lacks these brain clock neurons (Lehman et al., 1987). This result supported the idea that the SCN clock itself signalled rhythmicity to the body. About 17 years after the fly mutant had been identified, a major breakthrough came with the discovery of the first mammal, a hamster, bearing a clock mutation (Ralph & Menaker, 1988). This enabled a transplant study that provided very convincing proof that the SCN itself sets the period of rhythmicity because the restored circadian rhythm has the period of the donor rather than that of the host (Ralph, Foster, Davis, & Menaker, 1990). Importantly, in all these transplant studies, the restored functions include rhythmic

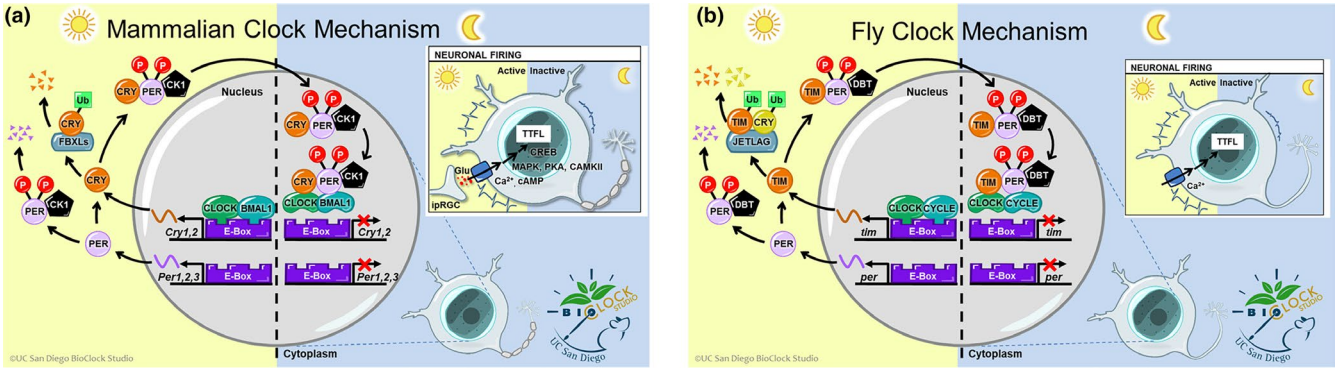

FIGURE 1 Comparison of the cellular molecular clock in mammals (a) and flies (b). (a) CLOCK and BMAL1 are transcription factors that form a heterodimer and bind to E-boxes in the nucleus to promote the expression of the *Per* and *Cry* genes during the day. PER and CRY act in the negative limb of the mammalian clock TTFL. The *Per* and *Cry* genes are transcribed to produce mRNA in the nucleus, which then travels to the cytoplasm to be translated into proteins. Forming a heterodimer with one another, PERs and CRYs form a complex and return to the nucleus to inhibit their own expression by binding to and inactivating CLOCK-BMAL1. Stability of PERs is regulated by casein kinases (CK1δ, CK1ε, CK2), enzymes that phosphorylate (P) PERs and promote PER degradation. Note that CK1 is a homolog of *Drosophila* double-time (DBT). Formation of a large complex of PERs, CRYs, and other proteins prevents their degradation. Stability of CRYs is regulated by F-box proteins (FBXLs: FBXL3, FBXL21), enzymes that add ubiquitin (Ub) chains and promote CRY degradation. A light signal is delivered from the retina to the SCN, the master circadian clock tissue of mammals, by intrinsically photosensitive retinal ganglion cells (ipRGC). Glutamate (Glu) release from ipRGCs excites SCN neurons. Neuronal excitation modulates the TTFL through a signalling pathway involving calcium and cyclic adenosine monophosphate (cAMP). In the downstream pathway, mitogen-activated protein kinases (MAPKs), protein kinase A (PKA) and calcium/calmodulin-dependent protein kinase II (CAMKII) are activated. Finally, cAMP response element-binding protein (CREB) activation modulates expression of several clock genes. Spontaneous firing of SCN neurons increases during the day and decreases during the night even without light signalling. Maintenance of proper membrane potential is necessary to generate circadian rhythms along with the TTFL. (b) CLOCK and CYCLE are transcription factors that form a heterodimer and bind to E-boxes in the nucleus to promote the expression of the Per and Tim genes during the day. PER and TIMELESS (TIM) act in the negative limb of the *Drosophila* clock translational transcriptional feedback loop (TTFL). They are transcribed to produce mRNA in the nucleus, which then travels to the cytoplasm to be translated into proteins. Forming a heterodimer with one another, PER and TIM return to the nucleus to inhibit their own expression by binding to and inactivating CLOCK-CYCLE at night. However, if PER does not form a dimer with TIM in the cytoplasm, DBT, a kinase that phosphorylates PER, will promote the protein's degradation. DBT travels into the nucleus with the PER-TIM heterodimer. CRY works as a blue-light sensor in the *Drosophila* TTFL. Once it is activated by sunlight, CRY will bind to TIM. The formation of the CRY:TIM complex promotes the recruitment of JETLAG, a ubiquitin ligase. The complex is then ubiquitinated by JETLAG to promote TIM and CRY's light-dependent degradation. In this way, light-activated CRY promotes TIM's degradation. Once TIM is removed, PER is degraded due to its instability when it is phosphorylated and not in complex with TIM. Spontaneous firing of fly clock neurons increases during day and decreases during night even without light signals. Maintenance of proper membrane potential is necessary to generate circadian rhythms along with the TTFL. Membrane potential controls the TTFL through signalling pathways involving calcium. *Re-printed with permission from: Lim, Mike, Tu, Christopher, Noguchi, Takako, and Golden, Susan S. 'Common clock mechanism graphics tool'. The BioClock Studio. http://ccb.ucsd.edu/_files/bioclock/projects-2017/clockmechanismgraphicstool_v1.0.pptx (accessed October 27, 2019)

locomotor activity, but no restoration of endocrine rhythms (Meyer-Bernstein et al., 1999). The explanation for this may lie in the output signals of the SCN. Locomotor activity rhythms may be the product of a signal that diffuses from transplanted tissue. This hypothesis is supported by evidence that transplants encapsulated in a polymer membrane are sufficient to restore locomotor activity rhythms (Silver, LeSauter, Tresco, & Lehman, 1996). Further evidence of the efficacy of diffusible signals comes from co-cultures of rhythmic and non-rhythmic tissues ex vivo (Honma, 2019; Maywood, Chesham, O'Brien, & Hastings, 2011; Ono, Honma, & Honma, 2016). Basically, the nature of SCN outputs is poorly understood, but there is accumulating evidence for humoral signalling (Honma, 2019; Maywood, 2019). The functional importance of the SCN is also underscored by classic studies that described how SCN-lesioned chipmunks in a natural environment are more likely to die from predation compared to surgical controls (DeCoursey, Walker, & Smith, 2000). Taken together, the lesion and transplant work highlight the importance of understanding not only the SCN as a 'master clock', but also inputs and outputs of this system.

A paradigm shift in understanding cellular clocks came in studies of individual cells. Once the field realized that the clockwork mechanisms were based on intracellular feedback loops, the question then became whether these twenty-four-hour oscillations were an emergent property of the SCN tissue-level network or whether it was a property of individual cells. In 1995, dispersed SCN neurons were shown to oscillate in vitro, suggesting that rhythmicity is a cellular property and not an emergent property of the circuit (Welsh, Logothetis, Meister, & Reppert, 1995).

Most shocking in its day was the subsequent discovery that rhythmicity was not restricted to SCN neurons but that 'oscillators are everywhere' (Balsalobre, Damiola, & Schibler, 1998; Zylka et al., 1998). This work set the stage for understanding phase relationships and synchrony of cells throughout the body—an important concept and a major topic of investigation today.

2.2 | Health consequences of circadian disruption

With the realization that cells throughout the body keep circadian time, it became clear that synchronization needed to occur between the organism and its environment. A mismatch between these compartments could have adverse health consequences. One of the earliest indications that circadian desynchrony between the organism and its environment could impair health was from work done in the first circadian mutant mammal (the tau mutant hamster). These animals with a genetically faster circadian clock (~22-hr period length in the heterozygote mutant) have lifespans that are more than 20% shorter that their wild-type conspecifics when housed in a standard 24-hr LD cycle (Hurd & Ralph, 1998). Interestingly, later research found the opposite effect on lifespan when animals are housed in constant dim light (Oklejewicz & Daan, 2002)—that is short-tau mutant hamsters lived longer than wild-type. It is likely that in LD conditions, in which the entire cycle is 24 hr ($T = 24$), heterozygous tau mutants must phase shift ~2 hr each day to stay entrained. These repeated phase shifts can decrease longevity. For example, repeated shifts of the LD cycle hasten tumour growth (Filipski et al., 2009), and mice with cardiomyopathy are more likely to die if housed in an environment with repeated inversions of the LD cycle (Penev, Kolker, Zee, & Turek, 1998). Moreover, repeated weekly advances of the LD cycle reduce survival of aged rats compared to controls in an unchanging LD cycle. The idea of dramatic health consequences of long-distance travel or shift work is supported by classic research in flies in which repeated phase shifts shorten lifespan (Aschoff, Saint Paul, & Wever, 1971). Taken together, this work shows that circadian misalignment between the organism and environment can cause circadian disruption that adversely impacts health.

A familiar example of circadian rhythmicity is the daily sleep–wake cycle. Insight into how the circadian system regulates the timing of sleep was provided in a model that considered two factors—namely, sleep debt and circadian rhythmicity (Borbely, 1982; Zhang & Fu, 2019). This model, depicted in Figure 2, suggests that a permissive window of sleep is provided by coincidence of a build-up of Process S (sleep debt) over the period of wakefulness and a decline of Process C (circadian rhythm of alertness/arousal). Process C continues to oscillate with a 24-hr period even under chronic sleep deprivation, and Process S is discharged or reset over the sleep duration period. The first indication that Process C had a genetic basis came in the discovery of several related individuals with extreme early awakening times and normal sleep duration (Jones et al., 1999). This syndrome, called Familial Advanced Sleep Phase, was later attributed to a mutation in *hPER2* gene that resulted in earlier nuclear entry and thus a shorter circadian cycle (Toh et al., 2001). This early work provided strong evidence for the interaction of the molecular circadian clock and the sleep homeostatic system.

In the context of disease, it has long been known that disruption of sleep–wake patterns are early symptoms. This link to mental health was described over a century ago in one of the first psychiatry textbooks in 1883 (Wulff, Gatti, Wettstein, & Foster, 2010). Correction of aberrant sleep–wake rhythms can be achieved through re-synchronization of the environment to the circadian timing system via appropriately timed light exposure (light therapy). In fact, light therapy was the first psychiatric treatment to be developed based on neuroscience and

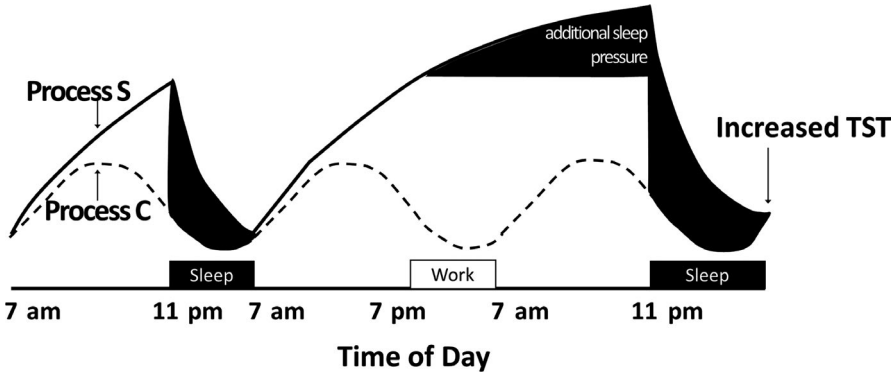

FIGURE 2 Two process model of sleep. Process S (Sleep) refers to the homeostatic process of sleep. Process C (Circadian) refers to the 24-hr rhythm in alertness driven by the internal clock. A permissive window of sleep occurs when C is low and S is high. Sleep pressure (the distance between Process C and S) continues to increase if sleep does not occur during the sleep window. Sleep pressure is lower after the missed night of sleep due to the increase in Process C. When sleep does occur, the duration is longer due to greater homeostatic sleepiness. TST: total sleep time. Modified from Borbely, 1982

not anecdotal observations (Wirz-Justice & Benedetti, 2019). These early attempts to use our knowledge of the circadian system to ameliorate symptoms of disease were the beginning of what we now call 'chronotherapy'. In fact, chronotherapy has gained tremendous importance. We now know something about the mediating mechanism—the circadian cycle gates the cell cycle (Levi & Schibler, 2007), and this knowledge has been useful in the treatment of cancer (Ballesta, Innominato, Dallmann, Rand, & Levi, 2017; Levi, 2002).

3 | SUMMARY AND CONCLUSIONS OF OVERVIEW

By 2017, decades of work had accumulated showing that essentially all cells of the body have a circadian clock mechanism (see Timeline in Figure 3) and that it is fundamental to understanding health, disruption of normal functioning and disease. As the Nobel jury stated, '… Their discoveries explain how plants, animals and humans adapt their biological rhythm so that it is synchronized with the Earth's revolutions'. Today, the outreach of timing in the circadian domain is extremely broad. Substantial fundamental and practical contributions are being made by many investigators from a range of scientific and medical backgrounds. Meetings of professional societies in the field include presentations by researchers studying diverse organisms from cyanobacteria and cockroaches to rodents and humans. Without question, one of the thrills of research in this area is that circadian timing is accessible to exploration at many levels of analysis from the subcellular to the whole organism in its interaction with its local environment. The circadian clock mechanisms can be analysed in many time domains ranging from seconds to hours, days, months and years. The impact of the work ranges from the bench to the bedside. Circadian organization is a ubiquitous property of life on this planet, and the effects of circadian timing on behaviour, physiology and in health and pathology have become ever more obvious. This Special Issue of EJN documents some of the supporting evidence. The many authors who contributed to this Special Issue present empirical work and/or review articles aimed at a general neuroscience audience. The topics highlight the major research developments, status and prospectus in the area. The broad impact of the circadian timing system can be appreciated in Table 1, which provides an overview of all the manuscripts and points to the invited contributing authors.

3.1 | Circadian rhythms in simple systems: why neuroscientists care

From the historical overview presented above, it is obvious that the study of circadian rhythms has successfully derived

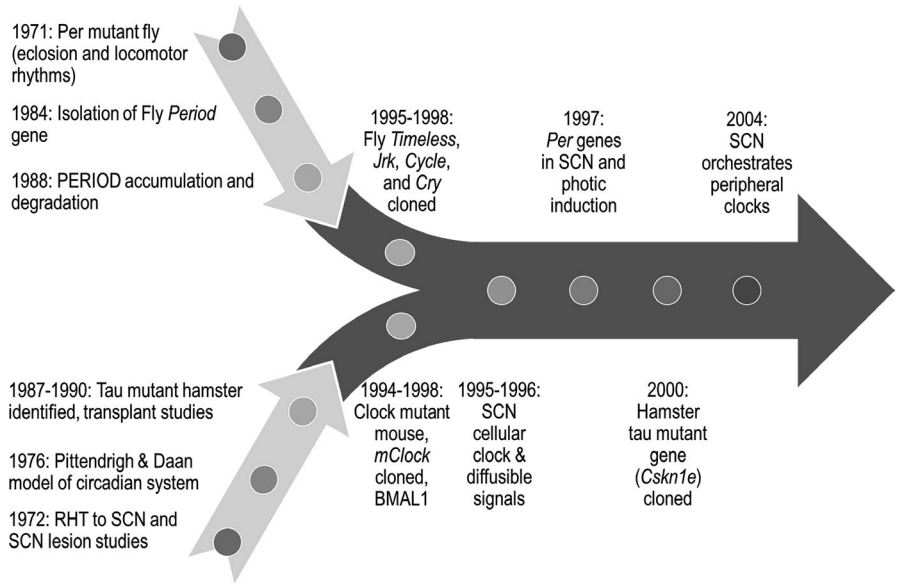

FIGURE 3 Timeline of landmark discoveries in chronobiology. See text for explanation. References: (Allada, White, So, Hall, & Rosbash, 1998; Antoch et al., 1997; Bargiello et al., 1984; Daan & Pittendrigh, 1976a, 1976b; Darlington et al., 1998; Gekakis et al., 1998; King et al., 1997; Konopka & Benzer, 1971; Lehman et al., 1987; Lowrey et al., 2000; Moore & Eichler, 1972; Moore & Lenn, 1972; Myers, Wager-Smith, Rothenfluh-Hilfiker, & Young, 1996; Myers, Wager-Smith, Wesley, Young, & Sehgal, 1995; Pittendrigh & Daan, 1976a, 1976b, 1976c; Price et al., 1998; Ralph et al., 1990; Ralph, Joyner, & Lehman, 1993; Ralph & Menaker, 1988; Sangoram et al., 1998; Shigeyoshi et al., 1997; Silver et al., 1996; Siwicki et al., 1988; Stanewsky et al., 1998; Stephan & Zucker, 1972; Sun et al., 1997; Tei et al., 1997; Welsh et al., 1995; Yoo et al., 2004; Zehring et al., 1984)

general principles applicable to nearly all species from findings in simpler model systems. It is generally accepted that circadian rhythms with fundamentally identical characteristics occur in all eukaryotes, with the caveat that relatively few organisms have been studied. In this issue, we have insights from three simple model systems, namely the cyanobacteria, a prokaryote (Golden, 2019), and eukaryotic organisms, yeast and *Neurospora* (Causton, 2019; Loros, 2019). The prokaryote *Synechococcus elongatus* circadian clock is the simplest known to date. It is made up of an oscillator based on three proteins named KaiA, KaiB and KaiC. This system permits examination of minimal requirements for oscillation in the face of mutations and alterations in the nutrient, thermal and photic environment (Golden, 2019). The work on the eukaryotic organisms, yeast and *Neurospora* again highlight rhythmic features that are conserved among organisms, each bearing specializations that contribute uniquely to our understanding. Baker's yeast have a cellular organization similar to that of higher organisms, with their genetic material contained within a nucleus. Nevertheless, they lack circadian rhythms and canonical clock proteins, but they undergo temperature-compensated rhythms in oxygen consumption that synchronize spontaneously when cells are grown in continuous culture. These properties enable the biochemical examination of metabolic oscillatory mechanisms (Causton, 2019). Work on *Neurospora* (Loros, 2019) takes advantage of the operating similarities among organisms underlying circadian clocks. In a simplified version, clocks are based upon a feedback loop, in which two proteins constitute a heterodimeric switch that drives expression of one or more genes. These gene products, in turn, act as negative elements to depress the activity of the transcription factor (the transcription, translation, feedback loop or TTFL). The result is the cyclic expression of clock genes and proteins. This system permits the examination of cues that set the phase of the internal clock, and it turns out that eukaryotic clocks can be reset through cues that affect the induction of negative elements in the feedback loop. The broad significance of the work comes from the notion that while genes involved are organism-specific, the organizing principles of clock-controlled gene output regulation are similar among eukaryotes.

4 | INVERTEBRATE AND MAMMALIAN CLOCKWORK

We now know that the fly clock is localized to a network of ~150 neurons with six clusters of neurons that express circadian clock genes (King & Sehgal, 2019). As noted above, the invertebrate molecular clock is highly evolutionarily conserved, likely due to its role in adaptation to the environment (see below; Helfrich-Forster et al., 2019). Not only is the molecular clockwork important for environmental adaptation, but it is also necessary for the neuronal activity rhythms of the small and large ventral lateral neurons (King & Sehgal, 2019). Clock neurons that express pigment-dispersing factor (PDF), an important output signal that drives rhythmic behaviour, are also GABA-sensitive (King & Sehgal, 2019; Stengl & Arendt, 2016). Variability of cockroach clock PDF-positive clock neurons in their response to GABA (including excitatory responses) is due to different combinations of GABA receptor subtypes and chloride co-transporters (Giese, Wei, & Stengl, 2019). Differential expression in these neurons likely influences gating of environmental inputs to the clock. Taken together, these results suggest that there is an intricate interplay between the environment, the molecular clockwork and the neurocircuitry that shapes appropriate behavioural responses in a way that is temporally appropriate.

Discoveries of the molecular clock in mammals have revealed the biochemical and structural complexity of the core clock components. This complexity turns out to be functionally important for timing. For example, the interactions between core and ancillary clock components such as epigenetic regulators and components of the activator or repressor complexes allow fine control of clock period and amplitude (Rosensweig & Green, 2019). These protein–protein interactions can also involve competitive binding which allows another layer of precision for time measurement. In addition to the physiological function of interactions of clock proteins with Per-Arnt-Sim (PAS) domains, pathological consequences can occur when environmental xenobiotics signal via aryl hydrocarbon receptor (AhR) activation (Tischkau, 2019). The molecular clock intersects with the AhR pathway to affect not only circadian timing but also pathology associated with circadian dysfunction (e.g. poor sleep, metabolic syndrome, cancer). In this issue, several authors document the evidence that an impaired molecular clock is an early indicator of declining health in diseases of the nervous system.

5 | MECHANISMS AND DEVELOPMENT OF THE CIRCADIAN TIMING SYSTEM

The ontogeny of the SCN and its chemical signals is a fascinating window into clock mechanisms. This is a particularly relevant topic at the present time as an increasing number of studies have established negative impact of early life circadian disruption on neural and behavioural development. The developmental time point at which circadian oscillations emerge is relevant. At the basic research level, we know that rhythmicity in the SCN is established before the formation of synapses (Moore & Bernstein, 1989). These alert us to the occurrence of mechanistic changes during development and ageing. These changes include developmental changes

in morphology, neurochemistry, interneuronal connectivity and efficacy of timing, all cues that influence the SCN. Considered in depth in this issue are classical findings and state-of-the-art research. The literature on pre- and perinatal development of the SCN and the ontogeny of its chemical signals is reviewed in Carmona-Alcocer, Rohr, Joye, and Evans (2019). In harmony, the development of the SCN intercellular network highlights an incredible battery of methodologies applied to deconstruct this clock system (Honma, 2019).

5.1 | Methodologies

As in all fields, the advent of new methods introduces both advances and controversies. Analysis of factors influencing clock oscillation has been advanced by the use of bioluminescent and fluorescent imaging of brain slices maintained in culture. A key assumption of this work is that the SCN when harvested from the anesthetized animal and studied ex vivo retains the properties that had been present in vivo (but see Leise et al., 2019). There are controversies in the development of SCN and its apparent functions, which arise in part, due to the use of various methods to detect SCN rhythms (Sumova & Cecmanova, 2019). These include in vivo studies based on behavioural assays of newborns, clock gene/protein detection in dissected SCN samples, and in vitro studies based on luciferase or green fluorescent protein reporter signals of cultured SCN explants.

6 | EXTRA-SCN OSCILLATORS

While the existence and locus of a brain clock in the SCN is no longer disputed, there remains a great deal unknown about its functioning and how it signals other regions of the brain. As already noted, key inputs to the SCN are photic phase setting signals that reach the SCN via a direct RHT. Importantly, the various cells of the retina and the retinal pigment epithelium themselves each bear circadian oscillators that communicate via synapses, gap junctions and released neurochemicals that can diffuse in the extracellular space outside of synapses. The consensus in the literature on the ways in which circadian signals are integrated in this highly organized retinal tissue is summarized in the paper by Ko (2019).

Highlighting a new realm of investigation, there is evidence of a contribution of a novel factor in SCN timekeeping—namely copper (Yamada & Prosser, 2019). Both background literature and new experimental results raise the possibility that copper is involved in light mediated glutamatergic resetting of the SCN. The role of trace metals is a new and emerging area of neurobiology in general, and the circadian system specifically, and the effects of exposure to trace metals in early development, remains to be examined.

Following up on their work related to redox and electrophysiological changes in relation to circadian rhythms, Naseri Kouzehgarani, Bothwell, and Gillette (2019) provide evidence of circadian variation in hippocampal redox in parallel with electrophysiological recordings. This work suggests a link to understanding the influence of redox on memory formation—a key function of the hippocampus. There is substantial evidence that there are molecular clocks in brain regions outside the SCN and it is important to understand how these transcriptional-translational clock gene rhythms are related to changes in the neurophysiology at different times of the day (Paul et al., 2019). The review provides a compendium of the evidence for extra-SCN oscillations, highlighting what is known of functions in different brain regions and where more work is needed.

7 | EVOLUTION AND ADAPTATION OF CLOCKS

While much work highlights evolutionarily conserved aspects of intracellular clocks, their evolution and diverse adaptations to local environments are also noteworthy. The nature of the evolutionary changes in clock genes and in the clock network in the brain of different Drosophilids may have caused behavioural adaptations in rest-activity patterns exhibited by flies that colonized different latitudes (Helfrich-Forster et al., 2019). For example, polymorphisms in and splice variants of clock genes allow adaptations to temperature and influence sensitivity to light. In addition, fly species that live in upper latitudes have altered rest-activity rhythms due to genetic modifications in CRY and PDF. This genetically determined behavioural pattern allows adaptation to varied environments including the harsh conditions of subarctic regions.

In mammals, one focus of research on evolution and adaptation has been drawn to the mechanisms underlying nocturnal versus diurnal activity patterns. These presumably emerged from pressures for seeking food and mates and for avoiding predators. It is surprising, however, that the timing of clock gene/protein expression in the SCN is not different between nocturnal and diurnal animals. Where in the brain do the differences between nocturnal and diurnal animals arise? A thorough review of the current state of knowledge regarding diurnal and nocturnal circadian timekeeping systems as it pertains to entrainment, masking and the adaptive significance of nocturnality versus diurnality is provided by Yan's team (Yan, Smale, & Nunez, 2019).

To find a mate and to produce young, the reproductive system must be synchronized to the environment, and behavioural and physiological mechanisms supporting mate-seeking, mating and producing young must all be synchronized. A classic example of circadian timing in the context of reproduction is the work of Everett and Sawyer (Everett & Sawyer, 1949) who

demonstrated a daily neural factor in the timing of ovulation over half a century ago. The trajectory from this initial description of an almost magical neural factor that determined the time of ovulation to an understanding of the contribution of the SCN is presented by Simonneaux (2019). In this work, our understanding of how the neuropeptide kisspeptin, first discovered in 2003, affects the hypothalamic–pituitary–gonadal axis to control daily and seasonal cycles is summarized. Since the time of Everett and Sawyer, the transcriptional control and synaptic mechanisms that are clock-controlled have developed into a huge dataset, with many authors working to integrate and share information. An emerging strategy is presented that not only surveys and integrates the literature, but also cross-lists rhythmic genes in the CircaDB database (Pizarro, Hayer, Lahens, & Hogenesch, 2013) with the synaptomeDB list (Pirooznia et al., 2012) for possible clock-controlled genes involved in synaptic transmission (Hannou, Roy, Ballester Roig, & Mongrain, 2019).

Given that females ovulate and males do not, there must be sex differences that support these functions. Relevant here is the fact that sex differences have been demonstrated in the circadian timing system. Thus, oestrogens (Hatcher, Royston, & Mahoney, 2019) and androgens (Karatsoreos, Butler, Lesauter, & Silver, 2011) can modulate the expression of clock genes in the SCN. Furthermore, these sex-typical steroids also modulate the expression of circadian locomotor behaviour (Model, Butler, LeSauter, & Silver, 2015) and alter sensitivity to photic cues (Butler, Karatsoreos, LeSauter, & Silver, 2012). For ovulation and fertility, a stable relationship between circadian timing systems and endocrine signals is required. Disruption of circadian rhythms by shift work, jet lag, etc., results in poor health outcomes, including deficits in reproductive outcomes.

The circadian timing system serves not only to synchronize daily rhythms to the environment, but also to anticipate regularly recurring events such as food availability (Mistlberger, 2011). Food is obviously a potent reward and food-seeking is mediated in part by the dopaminergic reward system. Not surprisingly, animals that exhibit unusual circadian timing patterns provide exceptional opportunities for exploration of anticipatory mechanisms and their evolution. Rabbits provide an example of a naturally occurring food anticipation paradigm. Dams leave their kits in the burrow and return to the burrow once daily for a very brief 3–5 min nursing bout. The babies require development of circadian timing in order to anticipate the appearance of the dams. The advantages of studying the rabbit as an experimental model for basic physiology and chronobiology, focusing on anticipatory activity and non-photic entrainment are reviewed by Aguilar-Roblero and Gonzalez-Mariscal (2019).

Dopamine has long been implicated in reward and timing systems (Burke & Tobler, 2016), and there has been consideration of its possible role in circadian timing. The link between circadian and interval timing mechanisms was assessed in a food anticipation activity (FAA) paradigm by LeSauter, Balsam, Simpson, and Silver (2019). The question addressed in this experiment was whether mice overexpressing the D2 dopamine receptor (D2R) in the striatum (only) display altered FAA. The results suggest that while FAA is altered in D2R-over-expressing mice, the effects are a consequence of reduced motivation. They found no evidence of altered interval or circadian timing behaviour and thus no support for a role of dopamine in timing.

7.1 | Circadian clock dysregulation impairs health

At its extreme, circadian dysregulation can produce poor health consequences. Thus, in flies, environmental circadian disruption impacts lifespan. This could be due to desynchronization of tissue-level clocks. Specifically, mice subjected to an LD cycle that is beyond the range of entrainment (20 vs. 24-hr days) experience continual phase advances and delays, and as a result, mice exhibit a weak behavioural rhythm (Leise et al., 2019). In this state, the time of dissection has a strong influence on the ex vivo phase of various tissues, causing phase shifts in organotypic cultures of SCN, adipose, and thymus from *Period2*$^{Luc/Luc}$ mice. These results suggest that a dampened intrinsic clock can dramatically affect the sensitivity to external stimuli (e.g., light) that shift the phase of the oscillator. In addition to aberrant LD cycles, circadian rhythms can be impaired through interaction with the sleep homeostat. In women undergoing a strict laboratory protocol, subgroups of metabolites (especially lipids) circulating in the blood vary over the circadian cycle; however, overall levels are also significantly decreased by sleep deprivation (Honma et al., 2019). Thus, this work in human subjects highlights sex differences in rhythmic metabolism that are modified by sleep.

Perhaps one of the greatest environmental disruptors of sleep and circadian alignment is shift work, which has metabolic and cardiovascular consequences. Working around-the-clock can result in circadian misalignment and sleep loss which then increase cardiometabolic risk (Kervezee, Kosmadopoulos, & Boivin, 2019). Strategies for reducing circadian misalignment-induced risk include targeting light/dark exposure, napping, physical activity, and meal timing. However, there is much variation in what researchers consider to be 'circadian disruption' as well as how this disruption should be experimentally measured in laboratory and field studies (Vetter, 2019). Chronobiologists must improve precision in the term 'circadian disruption'. The operational definition of this term affects experimental measurement of this disruption and what can be used as a proxy of circadian disruption in field settings. One intervention aimed at reducing social jetlag (defined as the mismatch between biological and

social time) is to block evening light with blue light blocking glasses (Zerbini, Kantermann, & Merrow, 2019). However, wearing these glasses in the evening advances the phase of melatonin and sleep onset on work days (only). As a result, this intervention does not improve social jetlag because sleep onset times do not change during weekends. Thus, much more work is needed on how we define and study circadian disruption and on finding solutions to ameliorate adverse effects.

7.2 | Mechanisms of sleep

In addition to orchestrating behavioural and hormonal rhythms, the circadian clock is critical for the timing of sleep, a state that is vulnerable to hazards in the environment. Studies of fruit flies have helped to tease apart the genetic and pharmacological underpinnings of this highly conserved physiological state. In this Special Issue, Hill, O'Connor, and Shirasu-Hiza (2019) review sleep behaviour in the context of circadian timing. In addition to a history of sleep research, the authors also discuss several theories for the purpose of sleep. For example, the Free Radical Flux Theory of Sleep is based on the recent work that oxidative stress disrupts sleep and that during sleep, macromolecules damaged by reactive oxygen species are cleared. Another important process that occurs during sleep is the reduction of overall neural activity and modulation of synaptic strength (Tononi & Cirelli, 2019). Specifically, the synaptic homeostasis model of sleep suggests one purpose of sleep is to protect neural coupling from overall synaptic down-scaling by maintaining neural activity of these coupled neurons during non-rapid eye movement sleep. This model could explain why sleep is critical for cognition. Finally, genetic variation and mutations have provided the underlying cause for some sleep disorders, including sleep problems associated with the circadian timing of sleep (advanced or delayed sleep phase), quality or duration of sleep, and insomnia (Zhang & Fu, 2019).

7.3 | Circadian dysregulation in disease

Disruption of sleep and circadian rhythms are often early indicators of many health disorders, and these disruptions further exacerbate the symptoms and pathology of disease. Often, the same neurotransmitter signalling pathways disrupted in disease are also either regulated in a circadian manner and/or are involved in the regulation of sleep and wake. Current research is aimed at going beyond a simple association by trying to pinpoint the timing of circadian disruption in the development of disease or identifying circadian disruption as a factor that hastens disease onset. For example, circadian dysfunction often precedes cognitive decline in Alzheimer's Disease (AD), and deficits in the SCN may underlie these symptoms. Likewise, accumulation of the AD neurotoxin amyloid-beta, may potentiate circadian disruption (Duncan, 2019). This bi-directional relationship between disorders, in general and circadian dysfunction points to the potential benefits of chronotherapy - the use of time-of-day to administer medication or treatment in order to enhance efficacy or reduce side effects (Abbott, Malkani, & Zee, 2019). A key concept is that treatments that ameliorate sleep and circadian rhythm disruption could slow disease progression or improve efficacy of other treatments.

Ageing is a normal part of developmental change, and thus, circadian clocks also change across the lifespan. Age-related clock dysfunction and strategies to reinforce circadian cycles in order to diminish these perturbations are reviewed by De Nobrega and Lyons, (2019). The authors point out that the fruit fly is a classic model that can be used to study the interactions between the circadian clock and age-related decline because of the short life span and the neurogenetic tools that are available (De Nobrega & Lyons, 2019). In mammals, ageing impacts SCN-regulated pathways, including sleep timing and entrainment to the LD cycle (Michel & Meijer, 2019). Specifically, electrical and neurochemical rhythms that are dampened in the aged SCN are due, at least in part, to an increase in firing of an anti-phased SCN neuronal subpopulation. These basic research findings may lead to novel anti-ageing therapeutic approaches such as bright light, melatonin, and exercise that may enhance SCN electrical rhythms and thereby ameliorate circadian deficits associated with age and age-related diseases.

In addition to ageing and neurodegeneration, psychiatric disorders are also known to be co-morbid with sleep and circadian rhythm impairment. We now know more about the underlying mechanisms for circadian regulation of mood via modulation of monoamine and glutamatergic transmission, HPA (hypothalamic–pituitary–adrenal) axis, metabolism, the microbiome, and/or neuroinflammation (Ketchesin, Becker-Krail, & McClung, 2019). Therapeutic advances and chronotherapeutics can be used to target underlying clock gene regulation, neurochemistry, cortical plasticity, neuroinflammation, and functional connectivity (Wirz-Justice & Benedetti, 2019). As mentioned earlier in this commentary, light therapy was the first psychiatric treatment to be developed based on neuroscience and not anecdotal observations, and non-pharmacological treatment for mood disorders has a foundation in sleep and chronobiology research (see Wirz-Justice & Benedetti, 2019).

7.4 | Future trajectory

What is the possible future trajectory of research in chronobiology? We can boast that research in this field has made

the leap from phenomenology to mechanism and has moved from bench to the bedside, the office, the shop and the home. Today, it is a 'hub' of scientific activity that cuts across research fields and study species. Detailed predictions are risky and inevitably wrong, but we have taken the risk to look into the future and imagine where inroads will be made (Table 2).

We offer a footnote: Clearly, there are a great many more contributors to our field than are represented in this 'special' Special Issue. We welcome additional insights into additional perspectives and alternative views/interpretations. A forum for comments is available in the *European Journal of Neuroscience* in *Neuro-Opinions*—a format that provides an avenue for continuing discourse.

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

TABLE 2 Future areas of investigation

Future areas of investigation
Timing of circadian disruption in disease progression
Basic research on circadian signalling pathways: in SCN and extra-SCN circuits
Chronotherapeutic, large-scale clinical trials on novel therapies
Research linking circadian neurosignalling, neuronal activity, and circadian behaviour
Novel sleep therapeutics need to incorporate effects on both homeostatic and circadian processes
Development of testable hypotheses for discovering the function of sleep
Discovery of novel dynamic interactions of molecular clock proteins
Research on the links between the molecular clock and non-circadian pathways disrupted in disease
More refined definitions of circadian disruption and circadian misalignment
Sex differences
Interventions: light/dark exposure, napping, physical activity, meal timing
Novel bioinformatic and analytical approaches to large datasets with circadian, temporal components
Novel strategies to understand relationship among spatial and temporal domains

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