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Neuronal oscillations on an ultra-slow timescale: daily rhythms in electrical activity and gene expression in the mammalian master circadian clockwork

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Abstract

Neuronal oscillations of the brain, such as those observed in the cortices and hippocampi of behaving animals and humans, span across wide frequency bands, from slow delta waves (0.1 Hz) to ultra-fast ripples (600 Hz). Here, we focus on ultra-slow neuronal oscillators in the hypothalamic suprachiasmatic nuclei (SCN), the master daily clock that operates on interlocking transcription-translation feedback loops to produce circadian rhythms in clock gene expression with a period of near 24 h (< 0.001 Hz). This intracellular molecular clock interacts with the cell's membrane through poorly understood mechanisms to drive the daily pattern in the electrical excitability of SCN neurons, exhibiting an up-state during the day and a down-state at night. In turn, the membrane activity feeds back to regulate the oscillatory activity of clock gene programs. In this review, we emphasise the circadian processes that drive daily electrical oscillations in SCN neurons, and highlight how mathematical modelling contributes to our increasing understanding of circadian rhythm generation, synchronisation and communication within this hypothalamic region and across other brain circuits.

Introduction

Neuronal oscillations or rhythms are integral to normal brain function and underlie the ever-evolving landscape of brain activity, brain states and behaviour (Engel *et al.,* 2001; Buzsaki & Draguhn, 2004; Buzsaki, 2015). These perpetual oscillations can be monitored from the scalp as electroencephalogram (EEG) and depict the synchronous activity of neurons that spans a number of brain region-specific frequency bands, from less than 0.2 Hz to frequencies in excess of 500 Hz (Lopes da Silva, 2013; Buzsaki, 2015). Intriguingly, these myriad rhythms can interact with one another through cross-frequency coupling, where oscillations with slower frequency drive and modulate the amplitude of faster local oscillatory events, while broadcasting to and recruiting larger networks of neuronal ensemble across the brain (Steriade, 2001; Csicsvari *et al.,* 2003; Sirota *et al.,* 2003; Buzsaki & Draguhn, 2004; Buzsaki *et al.,* 2012). Our increasing understanding is that these oscillations and their interactions shape and manage information flow in the brain, and are critical for healthy brain function (Basar-Eroglu *et al.,* 1996; Herrmann & Demiralp, 2005; Buzsaki *et al.,* 2012; Basar, 2013; Buzsaki, 2015).

This article focuses on the neuronal oscillations of the mammalian master circadian clock, the suprachiasmatic nuclei (SCN), which by comparison influence brain activity at a much slower frequency with a circadian period of near 24 h. We discuss some of the ionic, inter- and intracellular signalling, and molecular clockwork mechanisms driving the rhythmic excitability states of SCN neurons across the day–night cycle. In addition, we indicate how mathematical modelling is complementing and guiding some of the experimental work. This maturing synergy between experimental and computational methods is providing circadian biologists with invaluable insights into some of the circadian processes and mechanisms that otherwise would be impenetrable (Gonze, 2011b; Pauls *et al.,* 2016).

The SCN is a network of approximately 20 000 heterogeneous neurons coupled through chemical synapses, paracrine signalling and electrical gap junctions. A hallmark feature of SCN neurons, and one that is paramount to their collective functioning as the master circadian clock, is that their electrical activity shows spontaneous oscillation across the day–night cycle (Brown & Piggins, 2007; Colwell, 2011; Belle, 2015; Allen *et al.,* 2017); see Fig. 1. That is, these neurons are significantly more active during the day [an up-

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state with depolarised resting membrane potential (RMP) and generally discharging action potentials (APs) at ~ 4–6 Hz] than at night (a down-state with hyperpolarised RMP, firing at ~ 0.1–2 Hz or completely hyperpolarised-silent and not spiking; Fig. 1). Even when dissociated from the SCN network and dispersed *in vitro*, most SCN neurons retain their ability to generate this daily oscillation in excitability states for several days [e.g., see (Welsh *et al.,* 1995; Herzog *et al.,* 1998; Honma *et al.,* 1998; Shirakawa *et al.,* 2000; Aton & Herzog, 2005; Webb *et al.,* 2009)]. This indicates that most individual SCN neurons are intrinsic circadian oscillators, and while synaptic communication between the neurons is needed for synchronisation, it is largely not necessary for rhythms at the single-cell level. To achieve such evolving spontaneity in excitability across the circadian day, several intrinsic ionic membrane currents must interact (Bean, 2007; Llinas, 2014). Importantly, the magnitude of these currents and their interactions must also be appropriately tuned and sculpted across the 24-h period. The prevailing view is that these are achieved through the coordinated and cooperative activity of the molecular and membrane clocks (Colwell, 2011; Belle, 2015), see Fig. 2 and Modelling section 1.

The drive to peak excitation during the day

The depolarised RMP during the day (on average at ~ −45 mV) results from membrane excitation driven by several voltage-sensitive cation currents, including inward conductance provided both by sodium and calcium channels (Thomson, 1984; Wheal & Thomson, 1984; Thomson & West, 1990; Akasu *et al.,* 1993; Huang, 1993; Pennartz *et al.,* 1997; De Jeu *et al.,* 2002; Cloues & Sather, 2003; Jackson *et al.,* 2004; Kononenko & Dudek, 2004; Kononenko *et al.,* 2004; Paul *et al.,* 2016). Recently, through combined modelling and experimental work, a voltage-independent sodium channel (NALCN) was also identified as a positive driver for the SCN neuronal up-state (Clay, 2015; Flourakis *et al.,* 2015). Reduced global potassium channel activity during the day also contributes to the depolarised RMP (Jiang *et al.,* 1997; Kuhlman & McMahon, 2004). In particular, inhibition of the voltage-insensitive small-conductance calcium-activated potassium channels (SK_{Ca}) forces some SCN neurons to become hyperexcited (severely depolarised) and enter depolarisation blockade, a membrane state too positive (~ −30 mV) for AP generation (Belle *et al.,* 2009; Scott *et al.,* 2010; Diekman *et al.,* 2013; Belle, 2015; Paul *et al.,* 2016; Wegner *et al.,* 2017). Thus, these neurons either become completely silent or generate 2–7 Hz TTX-resistant, L-type calcium channel-dependent, depolarised low-amplitude membrane oscillations (DLAMOs) (Belle *et al.,* 2009; Diekman *et al.,* 2013; Belle & Piggins, 2017). Although the neurophysiological function of DLAMOs remains unknown, similar low-amplitude membrane oscillations are seen at more moderate RMPs (~ −45 mV) when TTX-sensitive sodium channels are pharmacologically blocked [TTX-LAMOs: see (Diekman *et al.,* 2013)]. These TTX-LAMOs arguably provide the underlying membrane rhythm for pacemaking activity in some SCN neurons (Jiang *et al.,* 1997; de Jeu *et al.,* 1998; Pennartz *et al.,* 2002; Jackson *et al.,* 2004). Indeed, mathematical modelling of experimental data shows that DLAMOs and TTX-LAMOs share similar neurophysiological characteristics and that the daily drive to hyperexcitation in SCN

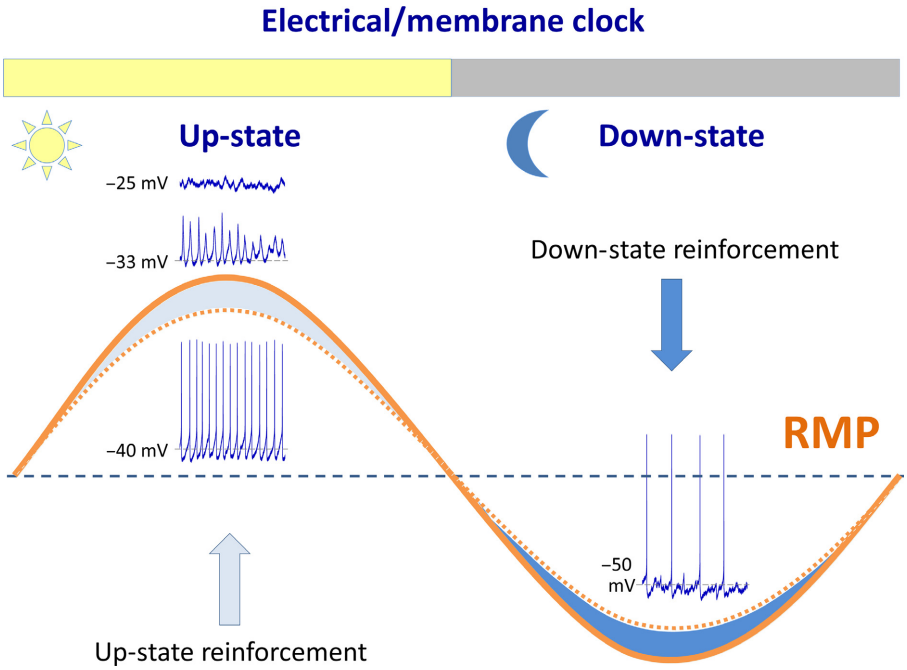

FIG. 1. A schematic overview of the excitability profile/waveform of suprachiasmatic nuclei (SCN) neurons over the day–night cycle. SCN neurons show overt oscillation in their resting membrane potential (RMP), traversing through points of neutral rest state (indicated by where the dashed blue line crosses the orange dashed and solid lines). The RMP of SCN neurons is depolarised (up-state) during the day and hyperpolarised (down-state) at night. In some neurons, the increased RMP elicits action potential (AP) discharge. In others, the RMP becomes too positive (~ −33 mV) to sustain AP production. These neurons display depolarised low-amplitude membrane oscillations (DLAMOs: ~ −33 mV) or become silent by depolarisation blockade (~ −25 mV). At night, the RMP reduces (~ −55 mV) causing SCN neurons to generate APs at lower rates or become completely silent by severe hyperpolarisation (~ −70 mV, not shown). Top yellow and grey bars represent the daytime and night-time, respectively. The blue arrow during the day represents extrinsic signals reinforcing SCN electrical up-state, and at night, the blue arrow represents physiological signals reinforcing SCN down-state (hypoexcitability). The light- and dark-blue shading areas, under and over the curve, show the differences in waveform amplitude between autonomous SCN activity (dashed line) and during appropriate daily reinforcement inputs.

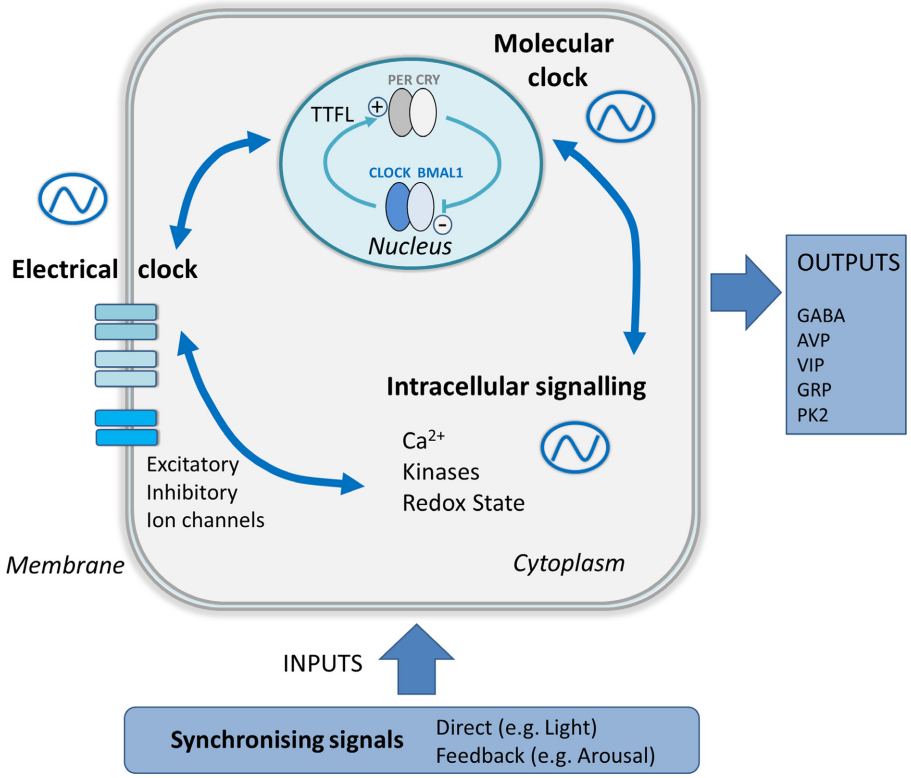

FIG. 2. A simplified schematic view of the intricate collaborative relationship between the molecular and electrical/membrane clocks for generating circadian rhythms/oscillations in the suprachiasmatic nuclei (SCN), and beyond. Within SCN neurons, autonomous molecular timekeeping signals generated by the transcription-translation feedback loop (TTFL) appropriately drive daily excitability and electro-responsiveness of the proximal membrane via intracellular signalling modulation of ion channel activity. Changes in membrane electrical activity feed back to sculpt and stabilise the molecular clockwork. This molecular/genetic-electrical interplay is dynamic and changes over the circadian cycle, temporally integrating time-adjusting cues from the light–dark cycle, physiology and behaviour. Thin intracellular blue arrows indicate direction of signal flow. Input and output signals to and from the SCN clockwork, respectively, are shown by extracellular thick blue arrows.

neurons may be paramount for circadian rhythm generation, maintenance and communication in this hypothalamic region (Diekman *et al.,* 2013; DeWoskin *et al.,* 2015).

In response to these moderately depolarised RMPs during the day, most SCN neurons generate 4–6 h of sustained spiking activity (Schaap *et al.,* 2003a; Welsh *et al.,* 2010). At the population level, this firing activity pattern collectively extends across the entire light phase of the circadian cycle, with peak firing frequency occurring in the middle of the day, around zeitgeber time 6-7 (ZT6-7, ZT0; time of lights on). This profile of activity has been measured extracellularly *in vitro* and in freely moving animals in several pioneering studies (Inouye & Kawamura, 1979; Green & Gillette, 1982; Groos & Hendriks, 1982; Shibata *et al.,* 1982; Gillette *et al.,* 1995; Schaap *et al.,* 2003b; VanderLeest *et al.,* 2007; Lucassen *et al.,* 2012), and in more recent years, with whole-cell electrophysiology and voltage-sensing genetic probe imaging (Morin & Allen, 2006; Brown & Piggins, 2007; Colwell, 2011; Belle, 2015; Allen *et al.,* 2017; Brancaccio *et al.,* 2017; Enoki *et al.,* 2017a, 2017b). To support the elevated firing frequency during the day, the activity and gating characteristics of several action potential-shaping potassium channels are appropriately regulated. This includes upregulation of the fast delayed rectifier (FDR) and A-type channels, and downregulation/modulation of the large-conductance calcium-activated potassium (BK_{Ca}) channel activity (Cloues & Sather, 2003; Itri *et al.,* 2005, 2010; Pitts *et al.,* 2006; Granados-Fuentes *et al.,* 2012; Montgomery & Meredith, 2012; Montgomery *et al.,* 2013; Whitt *et al.,* 2016).

Night-time silencing

Towards the end of the light phase, SCN neurons begin to traverse to the hypoactive down-state where most of these cells reduce their firing rate or become hyperpolarised-silent, ceasing spiking activity (Fig. 1). In some neurons, this represents an impressive 20–30 mV migration in RMP, when daytime and night-time rest state values are compared (Kuhlman & McMahon, 2004, 2006; Belle *et al.,* 2009; Paul *et al.,* 2016). Potassium channel activity is the main driver for this night-time silencing. For example, the outward conductance of potassium channels, such as BK_{Ca}, is known to increase during the night (Jiang *et al.,* 1997; Pitts *et al.,* 2006; Flourakis *et al.,* 2015; Whitt *et al.,* 2016). Further, SCN neurons show activity for the two-tandem pore domain potassium (K2P) channels (Wang *et al.,* 2012; Belle *et al.,* 2014). Although no biophysical and electrophysiological measurements of K2P channel activity are reported in SCN neurons across the day–night cycle, transcripts for these channels peak during the night (Panda *et al.,* 2002; Lein *et al.,* 2007). These voltage-independent potassium 'leak' channels contribute to RMP setting in neurons (Mathie, 2007). Thus, their activity in the SCN at night will contribute to membrane hyperpolarisation, placing SCN neurons into the down-state (see possible reinforcement by orexin-K2P channel activity below).

As a result, the average excitability waveform of the SCN neuronal ensemble across the day–night cycle is sinusoidal with a peak during the day and a trough at night, traversing two neutral rest states at dawn and dusk (Fig. 1). Incredibly, the overall timing and

half-width of this peak and trough in electrical activity follow day length/photoperiod, endowing the SCN with the additional ability to time and regulate important aspects of the body's seasonal rhythms, such as neuro-hormone secretion during the short winter and long summer days (Mrugala *et al.,* 2000; VanderLeest *et al.,* 2007; Welsh *et al.,* 2010; Coomans *et al.,* 2014).

The molecular clockwork: demonstrated as the driver of SCN electrical oscillations

Compared with some of the high-frequency rhythms that are measured elsewhere in the brain, SCN neurons are exceedingly slow oscillators. This is because the daily excitability cycle of SCN neurons is driven by an internal molecular clock which functions as an interlocking transcription-translation feedback loop (TTFL). Much is known about the intricate inner working of the TTFL molecular machinery which shares remarkable homology across species studied so far, from plants to insects, fish and mammals (Hastings & Maywood, 2000; Reppert & Weaver, 2002; Ko & Takahashi, 2006; Guilding & Piggins, 2007; Takahashi *et al.,* 2008; Glossop, 2011; Mohawk & Takahashi, 2011; Mohawk *et al.,* 2012; Buhr & Takahashi, 2013; O'Neill *et al.,* 2013; Partch *et al.,* 2014). At its core, the molecular clock in mammals includes a dynamic interplay between the protein products of canonical clock genes, such as *Period1/2* (*Per1/2*), *Cryptochrome 1/2* (*Cry1/2*), *Clock* and *Bmal1* (Fig. 2). The TTFL-clockwork is excellently reviewed in the above references and therefore will be fleetingly mentioned here. The 'positive arm' of the clock begins with the nuclear transcription and cytoplasmic translation of the proteins CLOCK and BMAL1. Once accumulated in the cytoplasm, they dimerise and the CLOCK/BMAL1 heterodimer then enters the nucleus and binds onto the promoter regions of the *Per1/2* and *Cry1/2* genes, activating their transcription (Fig. 2). The negative loop occurs when PER/CRY proteins dimerise, get phosphorylated by casein kinase 1 and translocated into the nucleus to suppress the CLOCK/BMAL1 activity, thereby terminating their own transcription. The overall interaction of these feedforward feedback loops drives perpetual rhythms in *Per1/2* and *Cry1/2* expression, with a peak during the day and a nadir at night, while *Bmal1* peaks at night and trough during the day [e.g. see Fig. 2 in (Guilding & Piggins, 2007)]. During the day phase of the cycle, the *Rev-erbα* gene is also transcribed and its protein product, REV-ERBα, acts in the nucleus to inhibit *Bmal1* transcription, forming an additional negative loop. Eventually, this *Bmal1* inhibition is lifted through PER/CRY suppression of *Rev-erbα* transcription, permitting BMAL1 to again slowly accumulate in the cytoplasm during the night phase.

Linking TTFL activity with excitability and behavioural rhythms

Although the mechanistic nature of the intracellular signals that interweave the molecular clockwork and membrane excitability in the SCN is still poorly understood, there is compelling evidence linking the activity of the molecular clock with membrane excitability oscillations in SCN neurons. The strongest indications come from studies assessing the effects of molecular clock mutations on the SCN temporal excitability profile. There is a clear relationship in wild-type animals between the period of the molecular clockwork, neuronal rhythms in the SCN and the animal's daily locomotor activity cycle. This link is highlighted/exposed when the activity of the molecular clock is astutely manipulated genetically. For example, in hamsters, a mutation in casein kinase 1 (the *Tau* mutation) shortens the period of neuronal oscillations (accelerates the speed of the clock) in the SCN, as measured by the timing in the daily peak of electrical activity (Liu *et al.,* 1997). This mutation also accelerates the locomotor activity rhythms in these animals (measured by wheel-running activity) by a factor that is representative of the period change in the SCN's electrical oscillations (Liu *et al.,* 1997). In mice, heterozygous *Clock* mutation lengthens behavioural and peak firing activity rhythms in the SCN (Herzog *et al.,* 1998; Nakamura *et al.,* 2002). Elimination of *Cry1* or *Cry2* activity lengthens and shortens the electrical and behavioural rhythms, respectively (Maywood *et al.,* 2011a; Anand *et al.,* 2013), while animals with *Cry1/2*, *Per1/2*, *Bmal1* deletion or homozygous mutations for *Clock* are completely arrhythmic with severe alterations in electrical firing patterns in the SCN (Herzog *et al.,* 1998; van der Horst *et al.,* 1999; Vitaterna *et al.,* 1999; Bunger *et al.,* 2000; Nakamura *et al.,* 2002; Bae & Weaver, 2007; van der Veen *et al.,* 2008; Pfeffer *et al.,* 2009). Further, delaying the degradation of CRY1 and CRY2 in mice lengthens the periods of the molecular clock, excitability rhythms in the SCN, and locomotor activity (Godinho *et al.,* 2007; Guilding *et al.,* 2013; Wegner *et al.,* 2017), whereas the *Tau* mutation of casein kinase 1 accelerates the clock and behavioural rhythms in these animals (Lowrey *et al.,* 2000; Meng *et al.,* 2008).

Further evidence linking the activity of the molecular clock with membrane excitability oscillations in the SCN comes from studies showing that the transcription activity and conductivity of several ion channels expressed by SCN neurons, such as L- and T-type calcium, BK_{Ca}, K2P, and voltage-gated and passive 'leak' sodium channels, are under circadian control (Panda *et al.,* 2002; Brown & Piggins, 2007; Colwell, 2011; Belle, 2015; Flourakis *et al.,* 2015; Whitt *et al.,* 2016; Allen *et al.,* 2017). Also, ion channel activity can be directly regulated by the TTFL components, such as the REV-ERBα regulation of L-type calcium channel activity (Schmutz *et al.,* 2014). In support, disruption in the activity of circadian clock's key molecular components perturbs ion channel function, leading to altered electrical activity in SCN neurons (Albus *et al.,* 2002; Colwell, 2011; Granados-Fuentes *et al.,* 2012). And finally, several intracellular signalling molecules that are associated with modulating membrane excitability in SCN neurons, such as cAMP, are also rhythmically regulated in the SCN (O'Neill *et al.,* 2008; Doi *et al.,* 2011).

The slow daily TTFL and electrical oscillations in SCN neurons are fundamental for providing appropriate circadian timing in physiology and behaviour, such as the sleep/wake cycle, feeding, hormone synthesis and secretion, and cardiovascular output (Kalsbeek *et al.,* 2006; Bechtold & Loudon, 2013; Miller & Takahashi, 2013; Belle, 2015). Having such a daily timer arms organisms with the capacity to predict recurring changes in the environment, an ability that is critical for survival; maximising feeding and reproduction while avoiding predation, for example (Pittendrigh & Minis, 1972; Saunders, 1972; Ouyang *et al.,* 1998; DeCoursey *et al.,* 2000; Spoelstra *et al.,* 2016). Indeed, for most species, the most relevant recurrent environmental change is the light–dark (LD) cycle, emerging from the earth's daily rotation about its axis.

Synchronisation and reinforcement of SCN neuronal oscillations by the environment and physiology

Although the daily excitability waveform of SCN neurons persists in the absence of external time cues (endogenous/free-running), their activity has to be synchronised and aligned with the animal's LD cycle. This ensures that the circadian timing signals communicated to the brain and body are in accordance with the external environment (see Modelling section 2). Our current understanding is that

under natural conditions, these neurons are entrained/synchronised by information on the intensity and spectral composition of ambient daylight (Walmsley *et al.,* 2015; Brown, 2016). This light information is conveyed directly to SCN neurons by the glutamatergic retino-hypothalamic tract (Lokshin *et al.,* 2015; Fernandez *et al.,* 2016) through the activity of specialised melanopsin-containing retinal ganglion cells (Meijer & Rietveld, 1989; Schmidt *et al.,* 2011; Lucas *et al.,* 2014). Although not all SCN neurons respond to light, a large proportion of cells are excited by this photic signal (Groos & Mason, 1978; Meijer *et al.,* 1989; Jiao *et al.,* 1999; Saeb-Parsy & Dyball, 2003b; Drouyer *et al.,* 2007; Brown *et al.,* 2011; Walmsley & Brown, 2015; Walmsley *et al.,* 2015; Tsuji *et al.,* 2016). Therefore, besides synchronising SCN activity, this extrinsic excitatory photic drive may also act to reinforce the TTFL-driven up-state of SCN neurons during the day.

Several internal physiological signals emerging from the body's arousal/wakefulness and homeostatic brain circuits feedback to influence circadian timing in the SCN [(Mrosovsky, 1996; Hut & Van der Zee, 2011; Hughes & Piggins, 2012; Belle, 2015; Meijer & Michel, 2015); see next section below]. These non-photic inputs include neuropeptide Y (NPY) neurons of the thalamic intergeniculate leaflet (IGL) which send axonal projections through the geniculo-hypothalamic tract (GHT), the serotonergic system of the raphe nuclei (Harrington, 1997; Morin, 2013), the basal forebrain cholinergic system (Bina *et al.,* 1993; Yamakawa *et al.,* 2016), as well as the arousal-promoting orexinergic neurons of the lateral hypothalamus (Mieda & Sakurai, 2012) which projects in the vicinity of SCN neurons (Date *et al.,* 1999; Belle *et al.,* 2014). In nocturnal rodents, a dark-pulse during the daytime causes increased locomotor activity together with a reduction of c-fos expression in the SCN (Marston *et al.,* 2008). This suggests that brain activity during arousal and wakefulness can feed back to suppress excitability in SCN neurons. Indeed, electrical recordings in behaving nocturnal rodents revealed that bouts of prolonged behavioural activity are associated with the immediate suppression of action potential discharge in the SCN, which remained stably suppressed throughout the duration of the behavioural activity (Yamazaki *et al.,* 1998; Schaap & Meijer, 2001; van Oosterhout *et al.,* 2012). It is therefore probable that in nocturnal animals, activity during wakefulness at night may serve as reinforcement for the TTFL-driven electrical down-state of SCN neurons. This is likely mediated through behavioural-dependent release of NPY and orexins in the SCN (Biello *et al.,* 1994; Belle *et al.,* 2014).

In support, exogenous application of NPY, serotonin, agonists for the acetylcholine receptors or orexins to SCN slices robustly suppress clock gene expression and excitability in SCN neurons (Liou & Albers, 1991; Shibata *et al.,* 1992; Prosser *et al.,* 1994b; van den Pol *et al.,* 1996; Cutler *et al.,* 1998; Gribkoff *et al.,* 1998; Farkas *et al.,* 2002; Brown *et al.,* 2008; Klisch *et al.,* 2009; Yang *et al.,* 2010; Besing *et al.,* 2012; Belle *et al.,* 2014; Belle & Piggins, 2017). Fittingly, when applied to SCN slices during the subjective night, orexin-A recruits the activity of potassium 'leak' channels to strongly suppress the RMP and spiking activity of SCN *Per1*-EGFP+ve neurons (Belle *et al.,* 2014); see also night-time silencing section above.

Despite differences in their temporal niche preference, clock gene expression and electrical activity in the SCN of diurnal and nocturnal animals show similar patterns of circadian oscillations (Kubota *et al.,* 1981; Schwartz *et al.,* 1983; Sato & Kawamura, 1984; Bae *et al.,* 2001; Mrosovsky *et al.,* 2001; Yan & Okamura, 2002; Caldelas *et al.,* 2003; Otalora *et al.,* 2013). This suggests that mechanisms acting downstream from the SCN are involved in determining animal's chronotype (Smale *et al.,* 2003). Nevertheless, results from the above studies make tantalising conjectures that suppressive behavioural inputs into the SCN are important in nocturnal animals to reinforce the night-time electrical down-state, while in diurnal species, up-state SCN activity is reinforced by excitatory photic inputs during the day.

To date, the effects of behavioural activity on SCN electrical output in diurnal species have not been comprehensively investigated. However, from our knowledge of the electrical rhythms in diurnal rodent SCNs we hypothesize that wakefulness and locomotor activity in these animals should provide excitatory inputs to SCN neurons. Under laboratory conditions, unlike in the wild, nocturnal animals are continuously exposed to ambient light during the day. It is therefore likely that, at least under laboratory conditions, light can act to reinforce SCN excitability during the day both in diurnal and nocturnal SCNs. The locomotor activity, on the other hand, reinforces SCN suppression in nocturnal animals at night while possibly supporting SCN excitability in diurnal species during the day.

Overall, these external and internal reinforcements are vital for normal SCN function as they collaborate with TTFL activity to ensure high-amplitude circadian oscillations in SCN excitability (van Oosterhout *et al.,* 2012), a neurophysiological requirement for good health, well-being and cognition (Ramkisoensing & Meijer, 2015). Indeed, this necessity for neuronal oscillation bolstering in the SCN by extrinsic signals is exposed during the ageing process. Here, the age-related dampening of SCN electrical rhythms, due to diminished TTFL outputs and neurochemical signalling, can be restored by daily voluntary exercise and exposure to bright light during the day (Schroeder & Colwell, 2013).

Glial reinforcement of SCN neuronal oscillations

Brain function occurs largely through the intricate and balanced synergistic relationship between neurons and neuroglia. In recent years, the role of glia in neuronal function has received renewed recognition with the discovery that astrocytes respond, synthesise and release many of the neurochemicals (known as 'gliotransmitters') that are pertinent in neuronal information processing (Cornell-Bell *et al.,* 1990; Fiacco *et al.,* 2009; Halassa *et al.,* 2009; Santello *et al.,* 2012; Verkhratsky *et al.,* 2012b). This raises the possibility that, besides maintaining homeostatic processes of the brain (sustaining energy balance, modulating synaptic/neurotransmitter activity and providing metabolic support), glial cells may have a more direct involvement in brain communication processes. Indeed, glial cells show fast intracellular calcium oscillations and can signal through vast network by gap junctions, shaping neuronal activity in the process (Verkhratsky & Kettenmann, 1996; Nedergaard & Verkhratsky, 2010; Nedergaard *et al.,* 2010; Verkhratsky *et al.,* 2012a). In the context of neuronal oscillations, recent pioneering studies have undeniably revealed a surprising role for astrocytes in information processing and cognitive behaviour. These studies found that astrocytic activity in the cortices of behaving animals shapes neuronal rhythm features in these brain areas to influence aspects of learning and memory (Lee *et al.,* 2014), and to appropriately switch cortical circuit rhythms into a synchronous sleep-like state (Poskanzer & Yuste, 2016).

The SCN have an elaborate astrocytic cell network (Guldner, 1983), which exhibits daily rhythms in glial fibrillary acidic protein (Lavialle & Serviere, 1993; Moriya *et al.,* 2000; Gerics *et al.,* 2006; Becquet *et al.,* 2008; Lindley *et al.,* 2008; Canal *et al.,* 2009; Womac *et al.,* 2009; Burkeen *et al.,* 2011), and metabolic activity (Schwartz & Gainer, 1977; van den Pol *et al.,* 1992; Lavialle &

Serviere, 1993; Womac *et al.,* 2009; Burkeen *et al.,* 2011). This SCN GFAP oscillation is sensitive to light, suggesting a possible role for glial involvement in SCN photic information processing. In support, the genetic disruption of GFAP activity in animals maintained under constant light conditions (LL) elicited profound alteration in locomotor activity (Moriya *et al.,* 2000). In addition, several lines of evidence suggest that astrocytes may influence the phase-resetting effects of light in the SCN by putative modulation of glutamatergic transmission at the retinal terminals (van den Pol *et al.,* 1992; Lavialle & Serviere, 1995; Tamada *et al.,* 1998; Moriya *et al.,* 2000; Lavialle *et al.,* 2001; Girardet *et al.,* 2010). Astrocytes are also known to rhythmically affiliate with dendrites of vasoactive intestinal polypeptide (VIP) and arginine vasopressin (AVP) SCN neurons across the day (Becquet *et al.,* 2008). Activity of these neurons promotes cell-to-cell synchronisation and circadian communication within the SCN, and beyond (see section below). Therefore, this daily fluctuation in glial-VIP/AVP neuronal contact may shape electrical activity in these neurons and, thus, supports circadian-relevant information processing in the SCN. In turn, VIP can dose-dependently influence the phase and amplitude of astrocytic rhythms (Marpegan *et al.,* 2009), and pharmacological blockade of metabolic activity in astrocytes alters electrical rhythms in the SCN (Prosser *et al.,* 1994a). Together, these results support that functional signalling between neurons and glia occurs in the SCN, but the role of glial communication in circadian timekeeping still needs in-depth investigation (Jackson, 2011).

Importantly, several studies have reported intrinsic daily oscillations in clock gene/protein expression in SCN astrocytes (Prolo *et al.,* 2005; Cheng *et al.,* 2009; Yagita *et al.,* 2010; Duhart *et al.,* 2013; Brancaccio *et al.,* 2017). This raises the possibility that the daily variation in SCN astrocytic clock activity contributes to overall circadian rhythm generation and communication in the SCN. Indeed, genetic disruption/manipulation of GFAP [(Moriya *et al.,* 2000), but only under LL)] and circadian clock gene (Brancaccio *et al.,* 2017) activities in SCN astrocytes produced profound alteration in locomotor activity, and in SCN neuronal clock gene and intracellular calcium oscillations (Barca-Mayo *et al.,* 2017; Brancaccio *et al.,* 2017; Tso *et al.,* 2017). Remarkably, clock gene expression in SCN astrocytes oscillates in antiphase to the rhythm in SCN neurons, peaking during the subjective night in astrocytes (Brancaccio *et al.,* 2017). This night-time peak in SCN astrocytic clock activity is associated with elevated extracellular glutamate level, which may favour an increase in inhibitory GABAergic tone in the SCN, primarily in the dorsal aspect (Brancaccio *et al.,* 2017). Novel mechanisms through which astrocyte activity transforms glutamatergic excitation into tonic GABAergic inhibition have been described elsewhere in the brain (Heja *et al.,* 2012). Such glial-dependent tonic inhibitory GABAergic activity may provide further reinforcement for the electrical down-state in the SCN at night.

Collectively, these studies provide strong evidence supporting a collaborative role for glia and neurons in circadian rhythm generation and communication in the SCN, and, likely, beyond. Further, as in the cortices, glial activity in the SCN may have the additional function in shaping neuronal oscillation features to promote/favour appropriate circadian information processing across the circadian day, such as entrainment, synchronisation and brain-wide/body-wide circadian rhythm communication.

Intra- and intercellular signalling

Elsewhere in the nervous system, oscillations in intracellular calcium signalling underlie most of the fast rhythms in neuronal excitability (Berridge, 1998, 2014). In SCN neurons, steady-state intracellular calcium $[Ca^{2+}]_i$ concentration/level oscillates in a circadian manner, peaking during the day and entering a nadir at night [(Colwell, 2000; Ikeda *et al.,* 2003a; Irwin & Allen, 2010; Enoki *et al.,* 2012; Hong *et al.,* 2012; Brancaccio *et al.,* 2013; Belle *et al.,* 2014; Ikeda & Ikeda, 2014; Noguchi *et al.,* 2017); but see (Ikeda *et al.,* 2003b)]. This peak in global SCN $[Ca^{2+}]_i$ anticipates the peak in electrical activity (Ikeda *et al.,* 2003a; Enoki *et al.,* 2017b), raising the possibility that the initial source of $[Ca^{2+}]_i$ in SCN neurons is largely through clock-operated intracellular calcium store release (COi-CaSR), and not through depolarised RMP- and action potential-evoked membrane calcium entry via voltage-gated calcium channels (VGCCs). In support, pharmacological blockade of VGCCs and voltage-gated TTX-sensitive sodium channels diminished the amplitude (by~ 30%) but does not completely abolish circadian rhythms in $[Ca^{2+}]_i$ (Ikeda *et al.,* 2003a; Enoki *et al.,* 2012).

Activation of the ryanodine receptors (RyR1 and RyR2) represents one of the key signalling pathways by which calcium is released from intracellular stores (Berridge, 1998). The transcripts and proteins for both receptor types are expressed by SCN neurons with RyR2 transcript and protein showing higher levels during the subjective day than at night (Diaz-Munoz *et al.,* 1999; Pfeffer *et al.,* 2009). Interestingly, pharmacological disruption of RyR function abolishes circadian rhythms in $[Ca^{2+}]_i$ level, electrical activity and behaviour (Ikeda *et al.,* 2003a; Mercado *et al.,* 2009), suggesting that this is a key link between the molecular and electrical oscillations in SCN neurons. Indeed, members of the molecular clock, *Bmal1* and *Cry1*, interact to modulate the activity of the RyR2 transcription (Pfeffer *et al.,* 2009; Ikeda & Ikeda, 2014), while pharmacological activation of the RyRs causes excitation in SCN neurons (Aguilar-Roblero *et al.,* 2007, 2016). Together, this suggests that clock-operated intracellular calcium store release contributes to the up-state of SCN neurons during the day.

As in all neurons, the depolarised RMP and increased action potential firing during the up-state cause further calcium influx in SCN neurons through VGCCs (Jackson *et al.,* 2004; Irwin & Allen, 2007). Pharmacological blockade of this TTX-sensitive extracellular calcium source interrupts the molecular clock and electrical oscillations (McMahon & Block, 1987; Yamaguchi *et al.,* 2003; Lundkvist & Block, 2005; Lundkvist *et al.,* 2005; Myung *et al.,* 2012; Enoki *et al.,* 2017b), suggesting that calcium entry through VGCCs also contributes to circadian rhythm generation in the SCN.

Suprachiasmatic nuclei neurons are neurochemically and functionally heterogeneous, forming distinct peptidergic clusters within the ventral, medio-lateral and dorsal aspects of the SCN. Broadly, ventral SCN neurons synthesise VIP, while cells in the medio-lateral region produce gastrin releasing peptide (GRP), and dorsal neurons contain and release AVP (Antle & Silver, 2005; Morin & Allen, 2006; Golombek & Rosenstein, 2010). Some SCN neurons also contain prokineticin 2 (PK2), cardiotrophin-like cytokine and the transforming growth factor α (Kalsbeek & Buijs, 1992; Kalsbeek *et al.,* 1993; Kramer *et al.,* 2001; Cheng *et al.,* 2002, 2005; Kraves & Weitz, 2006; Li *et al.,* 2006; Burton *et al.,* 2016). Collectively, most SCN neurons produce the neurotransmitter GABA and express $GABA_A$ receptors (Abrahamson & Moore, 2001; Belenky *et al.,* 2008). Here, GABA acts primarily on the $GABA_A$ receptors to cause excitation or inhibition in the SCN [see (Albers *et al.,* 2017) for a comprehensive review], presumably coreleased by the SCN peptidergic neurons. As demonstrated by most forms of neuronal synchronisation in the central nervous system, GABA-$GABA_A$ receptor signalling in the SCN acts to synchronise the activity of its neurons (Liu & Reppert, 2000; Shirakawa *et al.,* 2000; Aton &

Herzog, 2005; Evans *et al.,* 2013; DeWoskin *et al.,* 2015; Myung *et al.,* 2015). Signalling from VIP, GRP and AVP neurons intermingles with GABAergic activity across the day–night cycle, through poorly understood mechanisms, to organise and sustain the overall neuronal oscillation architecture of the SCN (see Modelling section 3), such as the phase relationship of its neurons (Harmar *et al.,* 2002; Albus *et al.,* 2005; Aton & Herzog, 2005; Brown *et al.,* 2005; Maywood *et al.,* 2006, 2011a; Hughes *et al.,* 2008; Kalsbeek *et al.,* 2010; Welsh *et al.,* 2010; Evans *et al.,* 2013; Freeman *et al.,* 2013; Fan *et al.,* 2015; Mieda *et al.,* 2015). This phase relationship is dynamic with tremendous plasticity, and varies with environmental conditions (VanderLeest *et al.,* 2007; Lucassen *et al.,* 2012). The GABAergic-neuropeptidergic communication conduits also act cooperatively with the light-input pathway to integrate and align the SCN's daily pattern of oscillations with external environmental signals and feedback inputs from physiology and behaviour. Together, this ensures that, at the population level, SCN neurons produce coherent and high-amplitude circadian rhythms that are representative of the animal's solar cycle and internal physiological demands. Such integrated outputs are in turn necessary for driving robust circadian rhythms across the brain and body.

Function of neuronal oscillations in the SCN

Despite running at a much slower pace, circadian neuronal oscillations in the SCN share some common underlying principles and functions with neuronal oscillators studied elsewhere in the brain. For example, neuronal oscillators have an inherent capacity to appropriately 'gate' or 'vary' their sensitivity to synchronising signals, otherwise known as 'bias input selection' [see (Hutcheon & Yarom, 2000)]. Similarly, SCN neurons show variation across the day in their sensitivity to inputs, such as environmental light and internal physiological signals. Pioneering studies investigating the effects of light on nocturnal rodents, for example, established that light exposure in the early night delays subsequent cycles in locomotor activity, during the late night advances locomotor rhythms, and light during the day has no shifting effect on behavioural rhythm phase (Decoursey, 1960, 1964; Daan & Pittendrigh, 1976). These patterns of temporal sensitivity to light can also be observed in diurnal species, including humans [(Hoban & Sulzman, 1985; Kas & Edgar, 2000; Mahoney *et al.,* 2001; Khalsa *et al.,* 2003); see also Fig. 1 in (Brown, 2016)]. Application of pharmacological mimics of the light-input pathways to living SCN slices, such as glutamate or the glutamate receptor agonists AMPA and NMDA, also causes phase shifts in the electrical rhythms that imitate the light-induced shifts in locomotor activity (Colwell & Menaker, 1992; Shibata *et al.,* 1994; Biello *et al.,* 1997; Ding *et al.,* 1998; Moriya *et al.,* 2000, 2003). Similarly, optogenetic manipulation of SCN activity causes phase shifts in electrical and gene expression rhythms both *in vivo* and *in vitro* (Jones *et al.,* 2015). This phase adjustment by light allows daily resynchronisation of SCN cells to the external light–dark cycle (see section above) and, in extreme situations, permits realignment of the circadian system following a drastic shift in the LD cycle, as is the case in humans when flying across time zones. Albeit, the SCN's slow oscillation means that resynchronisation to the new LD cycle takes several cycles to accomplish (Reddy *et al.,* 2002; Nagano *et al.,* 2003; Yan & Silver, 2004; Nakamura *et al.,* 2005; Davidson *et al.,* 2009).

By contrast, non-photic inputs produce phase shifts in the SCN that differ significantly from those produced by light [see Fig. 1 in (Albers *et al.,* 2017)]. These signals produce large phase advances in behavioural rhythms during the day and small phase delays during the night (Mrosovsky, 1988; Reebs & Mrosovsky, 1989; Mead *et al.,* 1992; Hastings *et al.,* 1998; Lone & Sharma, 2011; Polidarova *et al.,* 2011). These non-photic phase shifts of the circadian system have also been studied in humans (Redlin & Mrosovsky, 1997; Mistlberger & Skene, 2005). As with the glutamatergic agonist mimics of the light-input pathway, when the SCN are treated during the day with neurochemicals that are linked with non-photic signalling in this structure, such as NPY, large phase advances are seen in locomotor behaviour or SCN firing rate rhythms *in vitro* (Albers & Ferris, 1984; Huhman & Albers, 1994; Biello & Mrosovsky, 1996; Golombek *et al.,* 1996; Biello *et al.,* 1997; Besing *et al.,* 2012). Remarkably, excitatory photic and suppressive non-photic signals can interact with each other at the level of the SCN. Cancellation of non-photic resetting effects occurs during the day if the non-photic signal is followed by a light pulse, or glutamatergic receptor agonists (Biello & Mrosovsky, 1995; Biello *et al.,* 1997; Gamble *et al.,* 2004). Similarly, the phase-shifting effects of light or glutamatergic receptor agonists at night are attenuated if the light pulse or glutamatergic agonist application is followed by non-photic-associated signals (Ralph & Mrosovsky, 1992; Mistlberger & Antle, 1998; Yannielli & Harrington, 2000, 2001; Yannielli *et al.,* 2004).

These inputs modulate rather than dictate SCN function, and this amenability to appropriate phase modulation by external signals represents a canonical property of neuronal oscillators of the brain and one that is central to their function. The capacity for SCN neurons to maintain temporal sensitivity and phase-adjust their electrical rhythms to pharmacological mimics of the light and non-photic input pathways *in vitro* suggests that the mechanisms involved are largely confined within the SCN circuits. Emerging evidence also suggests that these processes are determined both by the molecular and excitability states of SCN neurons (Ding *et al.,* 1998; Pfeffer *et al.,* 2009; Belle & Piggins, 2017). Therefore, the daily oscillatory excitability patterns or waveform of the SCN (up-state during the day and down-state at night, see Fig. 1) determines when and how excitatory and inhibitory inputs are likely to cause significant adjustments to the SCN phase. Such gating properties are crucial, providing a mechanistic neuronal substrate that permits the animals to appropriately respond to potentially competing external and internal signals in order to organise physiology and behaviour.

SCN outputs: communicating circadian rhythms across the brain

Circadian rhythms generated by SCN neurons are communicated across the brain through a broad array of synaptic and paracrine neurochemical signalling, such as VIP, GABA, AVP and PK2 (Ralph *et al.,* 1990; Silver *et al.,* 1990, 1996; Tousson & Meissl, 2004; Morin & Allen, 2006; Maywood *et al.,* 2011b; Morin, 2013; Silver & Kriegsfeld, 2014; Belle, 2015). Many of the downstream targets, including cortical, thalamic, epithalamic and hypothalamic areas, also express clock genes with some showing semi-autonomous variation in clock activity (Guilding & Piggins, 2007; Guilding *et al.,* 2009, 2010; Mohawk *et al.,* 2012; Bano-Otalora & Piggins, 2017). Indeed, electrical activity measurement in some of these brain regions also shows daily patterns in neuronal firing rate that are linked with the molecular clock activity (Sakhi *et al.,* 2014a, 2014b). Arguably, this demonstrates that the influence of the molecular clock on neuronal excitability is not a unique feature of SCN neurons, but extends to other neuronal populations across the brain. Notably, the phasing of clock gene expression in some of these extra-SCN oscillators is aligned with the animal's locomotor

patterns and not with the SCN's phase. Ideal examples for this can be seen in the hippocampi of dual-phasing rodents, such as the *Octodon degus* and diurnal grass rat, A*rvicanthis niloticus*. In these dual-phasing species, hippocampal circadian gene activity peaks in phase with the animal's behavioural rhythm, that is coincidently in phase with SCN activity when the animals show a diurnal activity pattern, but establish an antiphase relationship when these animals shift their activity phase preference to the night (Ramanathan *et al.,* 2010; Otalora *et al.,* 2013). Indeed, hippocampal and SCN clock gene oscillations in nocturnal species occur out of phase, with hippocampal clock gene expression consistently peaking during the animal's active phase at night (Wakamatsu *et al.,* 2001; Wang *et al.,* 2009). This supports the view that extra-SCN oscillators provide brain region-specific circadian timing in neurophysiology, aligning appropriate neuronal activity rhythms with behavioural and physiological demands (Martin-Fairey & Nunez, 2014), such as for the support of hippocampal memory formation and persistence (Eckel-Mahan, 2012; Wardlaw *et al.,* 2014). Indeed, these semi-autonomous clocks form part of an extended brain-wide circadian timing circuit in which the SCN are the master pacemakers (Green *et al.,* 2008; Morin, 2013). Accordingly, some of these SCN target areas receive direct neuronal projections from the SCN, and collectively, they express receptors for the neurochemicals that are endogenous to SCN neurons, including receptors for VIP (VPAC2), AVP (V1a/b) and PK2 (Zhou & Cheng, 2005; Cheng *et al.,* 2006; Morin & Allen, 2006; Guilding & Piggins, 2007; Mohawk *et al.,* 2012; Sakhi *et al.,* 2014b; Belle, 2015; Burton *et al.,* 2016). The intricate neurophysiological processes and mechanisms through which SCN neurons dynamically sustain/shape circadian rhythms in these extra-SCN clocks, however, remain poorly understood (Fig. 3). Sadly, this knowledge gap is now hampering progress in our understanding of how chronodisruption impacts ailments, such as mental health, metabolic syndrome, Alzheimer's disease and cancer.

Indeed, in several of these brain regions, rhythms that occur at the circadian timescale coexist with neuronal oscillations happening at much faster rates. Good examples for this can be measured in hippocampal and thalamic neuronal ensembles, where exceedingly fast oscillations (at 0.1 to 500 Hz) are interlaced with rhythms sustaining a near 24-h periodicity (Colavito *et al.,* 2015; Loh *et al.,* 2015; Besing *et al.,* 2017; Chen *et al.,* 2017). It is noteworthy that at the population level, neurons of the SCN, and those of the IGL and dorsolateral geniculate nuclei, also produce faster-than-24-h isoperiodic, ultradian or fast narrowband oscillations in electrical activity (Groos & Hendriks, 1979; Miller & Fuller, 1992; Walsh *et al.,* 1992; Bina *et al.,* 1993; Zhang *et al.,* 1995; Pennartz *et al.,* 1998; Aggelopoulos & Meissl, 2000; Lewandowski *et al.,* 2000; Saeb-Parsy & Dyball, 2003a; Brown *et al.,* 2008; Sakai, 2014; Tsuji *et al.,* 2016; Storchi *et al.,* 2017). Recent work has also described neuronal discharge in the SCN with a harmonic distribution close to 30 Hz (Tsuji *et al.,* 2016), oscillations that normally frequent the thalamocortical systems. Remarkably, even when dispersed in culture, SCN neurons can sustain faster-than-24-h oscillations in firing rate at the single-cell level [firing burst rhythms of ~10 min in duration with interburst intervals of 20 to 60 min (Kononenko *et al.,* 2013)]. Elsewhere in the brain, when neighbouring neuronal rhythms with contrasting frequency bands occur within the same anatomical structure, they are normally associated with different brain states. Indeed, these oscillations can appropriately compete or interact with one another (Klimesch, 1999; Kopell *et al.,* 2000; Engel *et al.,* 2001; Steriade, 2001; Csicsvari *et al.,* 2003). In the SCN, how these neighbouring rhythms interact and whether they coalesce to influence circadian rhythm generation and communication in this hypothalamic structure are unknown and warrant detailed investigations.

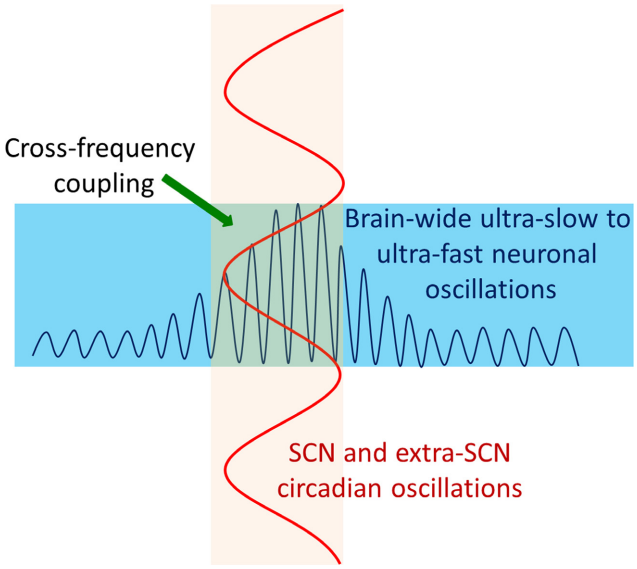

FIG. 3. A conceptualised schematic view of possible interactions between circadian rhythms and much faster neuronal oscillations in the brain, such as the fast rhythms of the hippocampus. The slow near 24-h rhythms generated by the suprachiasmatic nuclei (SCN) and/or extra-SCN oscillators interact with faster neuronal oscillations through cross-frequency coupling. This interaction influences the rhythm features, such as rhythm amplitude, of these faster brain oscillators. The detailed mechanisms involved remain elusive, but the concept presented here is based on our current understanding of neuronal rhythms interactions in the brain, and the circadian influence on ultradian corticosterone pulsatile release. Together, these may provide a glimpse into how these oscillations interact in the CNS in order to organise physiology and behaviour.

Nevertheless, the interesting observation that these faster ultradian and beta/gamma rhythms are more prominent during photopic than scotopic conditions suggests that they may play important roles in broadcasting and modulating environmental light information across the SCN circuits, and beyond. Indeed, many of the body's hormonal secretion profiles follow an ultradian rhythm (Bonnefont, 2010; Fitzsimons *et al.,* 2016). Our recent understanding of the intricate relationship between circadian and ultradian rhythms in daily corticosterone pulsatile release and activity provides a glimpse, perhaps, into how these oscillations may interact in the SCN and the brain for normal physiology [(Spiga *et al.,* 2014; Fitzsimons *et al.,* 2016); see Fig. 3 for a hypothesis]. As demonstrated elsewhere in the 'rhythm' fields, mathematical modelling will no doubt play a crucial role in shaping our understanding of such interactions and their physiological and behavioural relevance (see Modelling section 4).

Modelling section 1: mathematical modelling of the circadian clock at the single-cell level

One of the earliest models of biochemical oscillations incorporating the regulation of gene expression was introduced by Goodwin (Goodwin, 1965). This three-variable model, consisting of delayed negative feedback to a single gene, has been used by many researchers as a simple model of the mammalian molecular clock; see Fig. 4A (Ruoff *et al.,* 1999; Locke *et al.,* 2008; Woller *et al.,* 2013). The basic mathematical concept underlying these models is that delayed negative feedback can destabilise a steady state and

give rise to stable limit cycle oscillations through Hopf bifurcation (Forger, 2017). The only nonlinearity in the Goodwin model is the sigmoidal Hill function that characterises repression of transcription. Griffith showed that limit cycle oscillations are only possible in the Goodwin model with a Hill exponent $n > 8$ (Griffith, 1968). While such a large Hill exponent is unlikely to arise from cooperative binding of the repressor to the promoter (the typical interpretation for using $n = 3$ or 4 in enzyme kinetics) alone, other processes, such as multisite phosphorylation/dephosphorylation, could contribute to the sharpness of the protein activation function (Gonze & Abou-Jaoude, 2013; Woller *et al.,* 2014). Following the identification of several core clock genes, Leloup–Goldebeter and Forger–Peskin introduced detailed models incorporating these genes and their protein products (Forger & Peskin, 2003; Leloup & Goldbeter, 2003). The Leloup–Goldbeter retained the Hill function formulation of transcriptional regulation, whereas the Forger–Peskin model replaced Hill functions with first-order mass action kinetics. This results in a higher-dimensional model (73 differential equations in Forger–Peskin versus 16 in Leloup–Goldebeter), but fewer phenomenological parameters (such as Hill exponents) to estimate since all parameters now represent reaction rates. Development of new molecular models in both of these styles has continued as additional clock components and processes are characterised (Mirsky *et al.,* 2009; Relógio *et al.,* 2011; Kim & Forger, 2012; Jolley *et al.,* 2014; Woller *et al.,* 2016); see (Podkolodnaya *et al.,* 2017) for a recent review of this line of work. These models have made testable predictions that were validated experimentally, such as the short-period effect of the *Tau* mutation in hamsters (Gallego *et al.,* 2006). Detailed predictive models can provide insight into circadian clock mechanisms and evaluate competing hypotheses. For example, the Kim–Forger model has been used to argue that the key mechanism of transcriptional regulation in the mammalian clock is sequestration, and not multisite phosphorylation, of the repressor protein (Kim & Forger, 2012; Kim, 2016).

In comparison with the molecular clock, the electrical activity of mammalian clock neurons has received less attention from modellers. The first electrophysiological model of SCN neurons was developed by Sim and Forger (Sim & Forger, 2007) using the Hodgkin–Huxley formalism. The basic concept underlying conductance-based models is an electrical equivalent circuit representation of the cell membrane; see Fig. 4B. The Sim-Forger model was fit primarily to voltage-clamp data from dissociated SCN neurons (Jackson *et al.,* 2004), and included three voltage-gated currents (I_{Na}, I_{Ca} and I_K) and a passive 'leak' current (I_L). This model suggested that SCN neurons may enter depolarisation blockade at a certain time of day, a prediction that has since been validated experimentally (Belle *et al.,* 2009). Several authors have extended the Sim–Forger model to study various aspects of SCN neuronal activity, such as interspike interval variability due to stochastic openings of subthreshold voltage-dependent cation (SVC) channels (Kononenko & Berezetskaya, 2010), calcium-dependent inhibition of calcium influx through RNA editing of L-type calcium channels (Huang *et al.,* 2012) and nonlinear dependence of I_{Ca} on the Ca^{2+} driving force (Clay, 2015).

There are many ways in which the molecular clock may affect membrane excitability, such as by regulating the activation or inactivation properties of voltage-gated ionic channels. For example, Kononenko & Berezetskaya (2010) assumed that a circadian-regulated protein decreases the closed-time distribution of SVC channels (Kononenko & Berezetskaya, 2010). However, the most common way of connecting molecular and membrane models is to translate rhythms in mRNA levels of ion channel transcripts to rhythms in maximal conductances. As circadian changes in gene expression and protein abundance happen on a much slower timescale than the dynamics of action potential generation, one can model the electrical activity of SCN neurons over a short time interval by treating the gene and protein levels as parameters rather than dynamical variables. To simulate electrical activity at different times of day, the gene and protein parameters can be set in accordance with the phase of their daily rhythms. Viewed in this context, the maximal conductances of a Hodgkin–Huxley-type model become natural bifurcation parameters, and dynamical systems tools can be used to study transitions in SCN electrical activity over the course of the day. This strategy was used to interpret the DLAMOs observed in a subset of SCN neurons as evidence of the cells approaching a supercritical Hopf bifurcation due to increased g_{Ca} and decreased g_K (Belle *et al.,* 2009). The circadian variation in firing rate and resting membrane potential exhibited by SCN neurons is likely due to circadian variation in the conductance of several different types of ion channels (Kim & Jeong, 2008; Colwell, 2011). Flourakis *et al.* (2015) used a combination of experiments and modelling to show that antiphase rhythms in voltage-independent passive 'leak' currents, with sodium leak upregulated during the day and potassium leak upregulated at night, could reproduce the observed circadian variations in firing rate of SCN neurons. Furthermore, this 'bicycle' mechanism of antiphase regulation appears to be conserved in flies and mice.

A few models have dynamically integrated gene regulation and electrical activity at the single-cell level. Vasalou and Henson combined the Leloup–Goldbeter model of the molecular clock with an electrophysiology model based on the integrate-and-fire formalism (Vasalou & Henson, 2010). In this framework, circadian variation in ionic conductances leads to daily rhythms in variables representing RMP and firing rate. However, the model evolves on a timescale of minutes rather than milliseconds and therefore does not actually produce individual spike events (action potentials). Diekman *et al.* (2013) combined a modified version of the Sim–Forger model of action potential generation with a Goodwin-like model of gene regulation. In both the Vasalou–Henson and Diekman *et al.* models, intracellular calcium serves as the link between membrane dynamics and gene expression. The additional layer of feedback that comes from coupling membrane excitability to transcription can induce circadian oscillations in gene expression in a model of the molecular clock with parameters set such that it does not oscillate in the absence of excitation–transcription coupling (see Figs. 4C and 5). This supports the notion that SCN electrical activity may not just be a circadian output signal but also part of the clock's timekeeping mechanism, conceptualised here as the membrane clock.

Modelling section 2: mathematical modelling of circadian entrainment

There is a long history of mathematical modelling to aid understanding of how circadian oscillators (with periods near but not equal to 24 h) entrain to 24-h environmental cycles (Pavlidis, 1978; Winfree, 2001; Gonze, 2011a). Models predating the discovery of the suprachiasmatic nuclei and the transcriptional-translation feedback loops underlying the molecular clock were necessarily phenomenological rather than mechanistic. Wever used a modified version of the van der Pol oscillator to study re-entrainment of circadian rhythms following phase shifts of the light–dark cycle (Wever, 1966). Kronauer and colleagues further modified the van der Pol model to match experimental data on human circadian rhythms (Kronauer, 1990; Forger *et al.,* 1999). Variants of the Kronauer model are still being used to explain properties of jet-lag and to

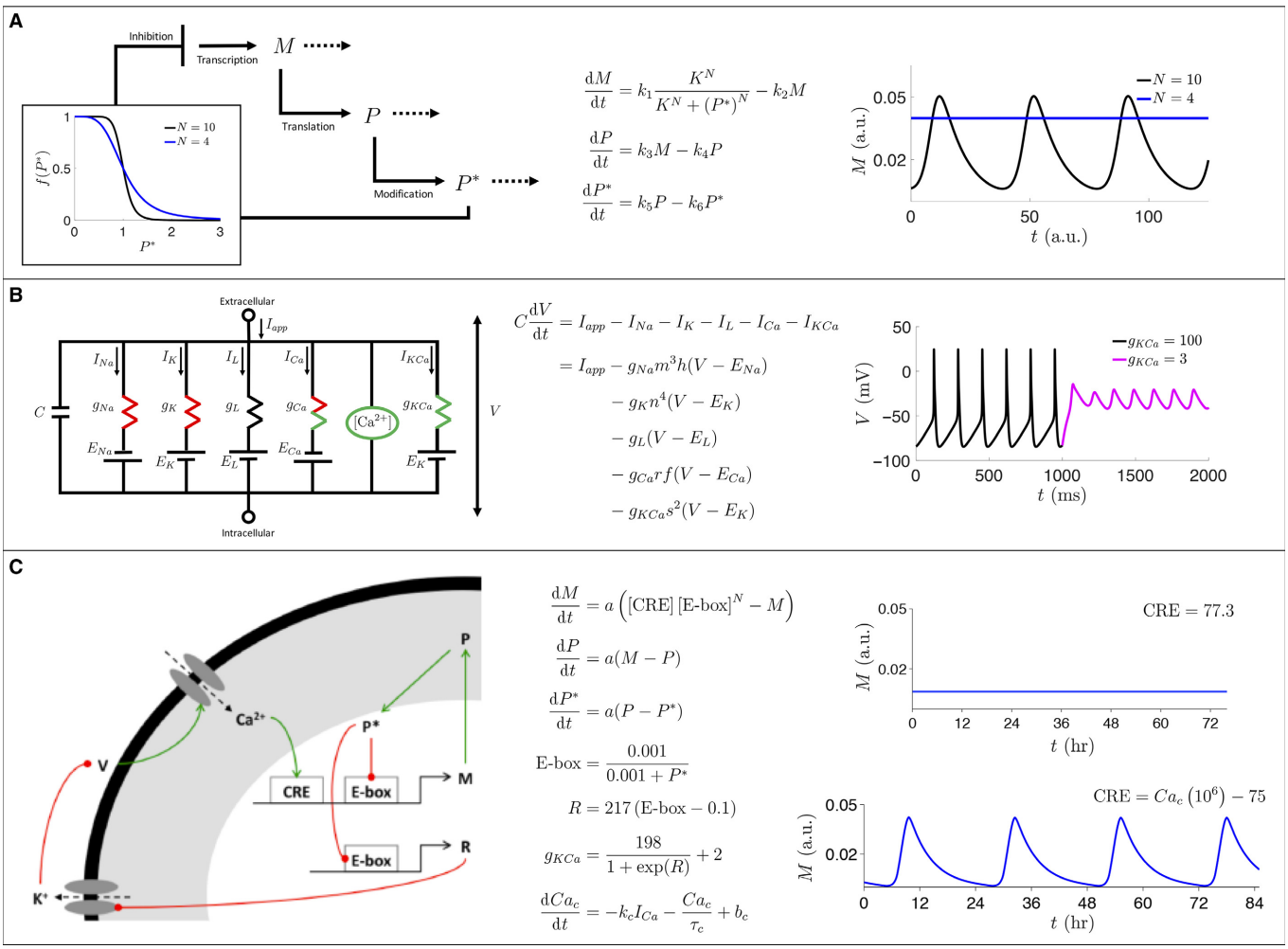

FIG. 4. Schematic overview, main equations and sample output for models of the molecular circadian clock (A), the electrophysiology of suprachiasmatic nuclei (SCN) neurons (B), and the interaction between circadian gene expression and SCN electrical activity (C). A: Goodwin model of gene regulation. A gene is transcribed into mRNA (*M*) and translated into protein (*P*), which undergoes posttranslational modifications (*P**) and is imported back into the nucleus where it inhibits production of *M*. This negative feedback loop can lead to oscillations in mRNA and protein levels if the Hill exponent (*N*) in the transcription repression function $f(P^*)$ is large enough. The dashed arrows represent mRNA and protein degradation. B: Hodgkin–Huxley-type model of neuronal excitability. The membrane voltage (*V*) is governed by a current-balance equation involving the cell capacitance (*C*) and ionic currents (I_x for ion *x*), described by a conductance (g_x) multiplied by a driving force ($V - E_x$), where E_x is the reversal potential of the ion channel. The sodium (Na), potassium (K) and calcium (Ca) channels are voltage-gated, with activation (*m*, *n*, *r*) and inactivation (*h*) gating variables that open/close as functions of voltage (red resistors). The activation gating variable (*s*) of the calcium-dependent potassium channel (KCa), as well as the inactivation gating variable of the calcium channel (*f*), are functions of intracellular calcium concentration [Ca^{2+}] (green resistors). The conductance of the leak channel (*L*) is passive, that is, not voltage- or calcium-dependent (black resistor). The differential equations describing the dynamics of the gating variables are not shown. This system of ordinary differential equations (ODEs) simulates how membrane voltage evolves over time and can produce both repetitive firing of action potentials (g_{KCa} = 100 nS) and depolarised low-amplitude membrane oscillations (DLAMOs; (g_{KCa} = 3 nS). C: Extended gene regulation model incorporating electrophysiology. Another gene product (*R*) is under the control of the same enhancer (E-box) found in the promoter region of the circadian clock gene that is transcribed into *M*. *R* downregulates the activity of potassium channels, which depolarises the membrane potential (*V*), leading to calcium influx through I_{Ca}. Higher levels of intracellular calcium (Ca_c) can activate transcription through the cAMP response element (CRE) pathway. Modelling CRE-dependent transcription as a function of Ca_c (bottom right inset) provides an additional layer of feedback control from membrane excitability onto gene expression and induces oscillations in mRNA concentration (*M*, arbitrary units), whereas modelling CRE activity as constant (top right inset) does not produce oscillations. In both cases, the Hill exponent representing cooperativity of repression at the E-box is set at *N* = 4.

design optimal schedules for fast re-entrainment following transmeridian travel (Serkh & Forger, 2014; Diekman & Bose, 2017). The process of re-entrainment has also been studied in more detailed models of the SCN network (Kingsbury *et al.,* 2016), and hierarchical systems with internal desynchrony between the SCN and clocks in peripheral organs (Leise & Siegelmann, 2006). An area requiring further work in the context of re-entrainment is the incorporation of homeostatic sleep drive and the gating of light input due to sleep (Booth *et al.,* 2017; Skeldon *et al.,* 2017). Classical dynamical systems tools such as phase response curves and Arnold tongues (Bordyugov *et al.,* 2015), along with the more recently developed methods of velocity response curves (Taylor *et al.,* 2010), macroscopic reduction of coupled phase oscillators (Hannay *et al.,* 2015; Lu *et al.,* 2016), and entrainment maps (Diekman & Bose, 2016), can provide insight into how entrainment properties of circadian oscillators depend on internal and external parameters, such as the oscillator's endogenous period, the environmental light intensity and daylength.

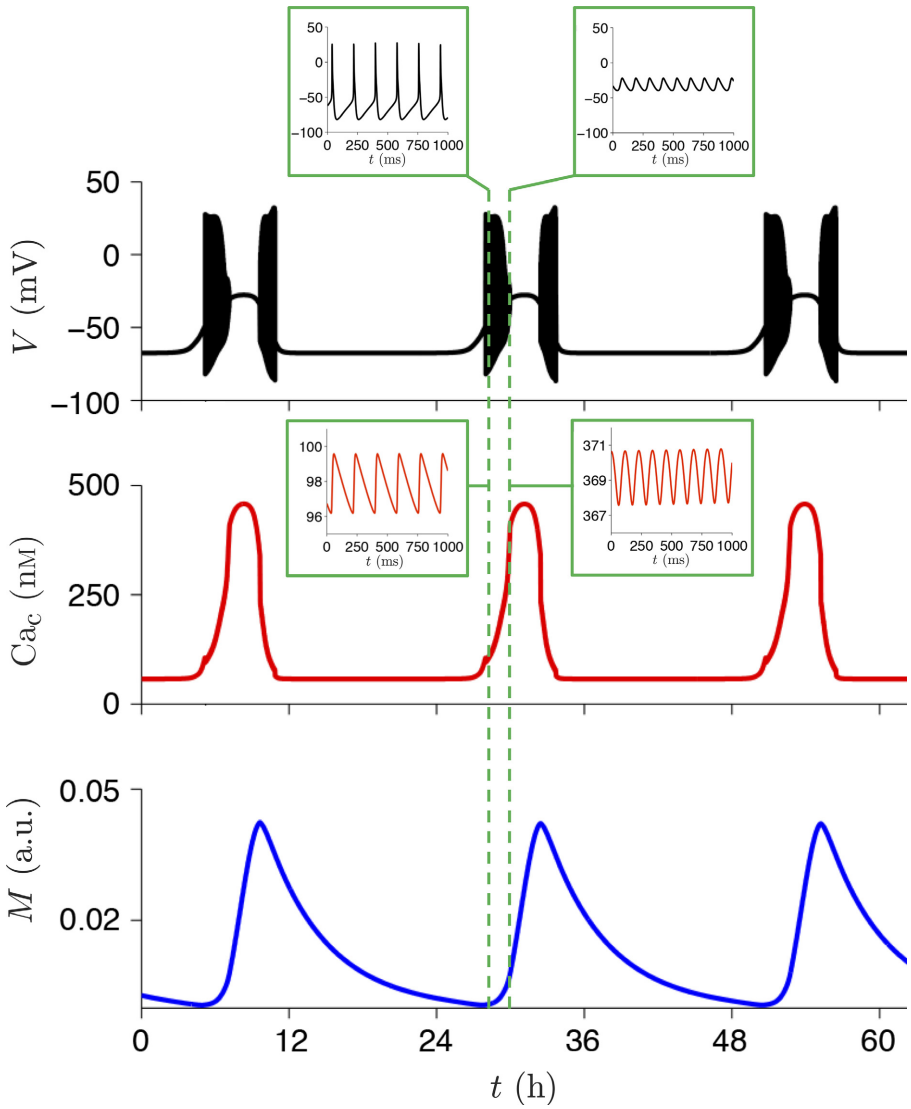

FIG. 5. Computer simulations of a multiscale mathematical model of suprachiasmatic nuclei (SCN) neurons integrating membrane excitability, intracellular calcium dynamics and gene regulation (see Fig. 4C). The membrane potential (V, thick black trace) exhibits a daily oscillation traversing several different electrical states on the timescale of hours. Embedded within the daily rhythm are oscillations on a much faster timescale (milliseconds), such as repetitive firing of action potentials at 6 Hz (top left inset) and DLAMOs (top right inset). These rhythms in RMP drive oscillations in intracellular calcium concentration (Ca_c) on both the daily (thick red trace) and millisecond (above left and right insets) timescales. The calcium rhythm induces a daily oscillation in gene expression [mRNA concentration M (arbitrary units), thick blue trace]. In turn, the gene expression rhythm regulates ion channel conductances that coordinate to produce the daily oscillation in membrane potential. This figure is adapted from (Diekman *et al.,* 2013).

Modelling section 3: mathematical modelling of the circadian clock at the network level

How the neurons within the SCN form a tissue-level clock capable of entraining to 24-h environmental rhythms and communicating this time-of-day information to other parts of the brain and body remains a fundamental question in the circadian field. As is the case for single-cell models, network models of the SCN exist at varying levels of biophysical detail. On the abstract end of the spectrum are models that view the SCN as a weakly coupled network of phase oscillators (Liu *et al.,* 1997). However, generic amplitude–phase oscillators may be more appropriate than pure phase models (Bordyugov *et al.,* 2011), as it has been shown that the amplitude of circadian oscillations can affect entrainment behaviour (VanderLeest *et al.,* 2009). Networks of modified van der Pol oscillators with local coupling (Kunz & Achermann, 2003), or daily inputs from non-rhythmic 'gate' cells (Antle *et al.,* 2003), have also been explored. Gonze *et al.* (2005) studied a network of Goodwin-like genetic oscillators globally coupled by a generic neurotransmitter. Many network models have since been developed incorporating more detailed descriptions of clock gene regulation, intercellular signalling cascades, and coupling architecture [for a review, see (Henson, 2013)]. For example, To *et al.* (2007) employed the Leloup–Goldbeter model of the TTFL, then added VIP/VPAC2 signalling, and a network with coupling strengths inversely proportional to the distance between cells. Bernard *et al.* (2007) used a molecular clock model that produces damped oscillations in the absence of coupling (Becker-Weimann *et al.,* 2004) and tested the effects of random sparse coupling, nearest-neighbour coupling, and an SCN-like combination of random sparse and nearest-neighbour connections. The

Vasalou–Herzog–Henson model included both VIP and GABA signalling, and mimicked the spatial organisation of the SCN by using small-world coupling for the ventral core region and nearest-neighbour coupling for the dorsal shell region (Vasalou *et al.,* 2011). This model also included an electrophysiology component that accounted for the effect of various ion channels and synaptic currents on each cell's firing rate, but did not simulate individual action potentials. Similarly, Bush and Siegelman used the leaky integrate-and-fire formalism and a two-variable model of the molecular clock to investigate the interaction of gene expression and firing rate in a small-world SCN network (Bush & Siegelman, 2006). Diekman and Forger modelled action potential generation in the SCN network with Hodgkin–Huxley-type neurons and GABA synapses. However, this model did not include dynamics of the molecular clock (Diekman & Forger, 2009). DeWoskin *et al.* (2015) developed the first network model of the SCN that resolves individual action potentials and intracellular molecular clock mechanisms. This model predicts that tonic GABA release at depolarised resting membrane potentials (during hyperexcitation) can phase shift the molecular rhythms and affects SCN synchrony. This highlights the importance of hyperexcitation in SCN neurons during the day.

Modelling section 4: future directions for mathematical modelling of the circadian system

In contrast to the prevalence of phenomenological and molecular models of the circadian clock, electrophysiological modelling of the SCN network is relatively nascent. The mechanisms by which the release of GABA, VIP, and other neurotransmitters and neuropeptides coordinate the daily electrical and gene expression rhythms of SCN neurons in the dorsal shell and ventral core are still poorly understood. Multiscale models of the SCN have the potential to generate experimentally testable predictions regarding rhythm generation across the network, inspired by the role that the interaction of modelling and experiment has played in distinguishing the ING (interneuronal network gamma) and PING (pyramidal-interneuronal network gamma) mechanisms of gamma oscillations (Whittington *et al.,* 2000; Tiesinga & Sejnowski, 2009; Wang & Buzsáki, 2012; Börgers, 2017).

In this review, we have primarily discussed models consisting of deterministic systems of ordinary differential equations (ODEs). Figure 6 provides a visual summary of the degree to which detailed molecular clock and electrophysiological mechanisms were incorporated into each of these models. Stochastic single-cell and network models have also been developed (Forger & Peskin, 2005; Ko *et al.,* 2010; An *et al.,* 2013) to explore the robustness of circadian rhythms to intrinsic and extrinsic sources of noise, but these have yet to be combined with electrophysiological models. ODE models, whether deterministic or stochastic, also neglect the spatial aspect of mRNA and protein molecules moving throughout the cell. Thus, partial differential equation (PDE) models incorporating reaction-diffusion may be useful for making quantitative predictions about spatial dynamics of the molecular clock. Nonetheless, ODE models have been able to explain certain features of spatial patterning in the SCN, such as why clock gene expression in the dorsal region phase leads the ventral region (Myung *et al.,* 2012). Aside from dynamical modelling, machine-learning algorithms have also been used to analyse how the spatial architecture of the SCN contributes to robust rhythm generation (Pauls *et al.,* 2014).

Beyond circadian rhythms, other biological oscillations involve the feedback between gene expression and electrical activity, for example the pulsatile release of GnRH every 90 minutes. Lightman and colleagues (Spiga *et al.,* 2015) have developed mathematical models to explore the interaction between the circadian clock and this ultradian endocrine rhythm. Furthermore, a mathematical modelling study of pancreatic islet β-cells has shown that calcium-dependent transcription can adjust potassium channel activity to rescue electrical bursting and insulin oscillations (Yildirim & Bertram, 2017). Circadian rhythms also modulate cortical excitability and EEG synchrony (Ly *et al.,* 2016). Chellappa *et al.* (2016) used neural mass modelling and the dynamic causal modelling (DCM) framework to demonstrate a strong circadian influence on cortical excitation/inhibition balance and gamma oscillations. Recent modelling and experimental work has also suggested that the circadian phase distribution of neurons in the hippocampus can support memory formation (Eckel-Mahan, 2012; Damineli, 2014). Damineli coined the term '*Tau* wave' to describe the temporarily coherent phase clusters with an approximately 24-hour period that emerged in his model of memory trace formation. As *Tau* is often used to denote the intrinsic period of a circadian oscillator, this term nicely emphasises the commonality between brain rhythms on the ultraslow timescale and faster neuronal oscillations, such as alpha, beta, gamma, delta, mu and theta waves/oscillations. Future work integrating circadian components into models of neuronal oscillations on faster timescales could reveal new insights into daily regulation of a variety of brain functions.

Conclusion and perspectives

Neuronal oscillations in the master mammalian daily clock generate and broadcast circadian timing across the brain and body. These synchronising signals shape the spatiotemporal architecture of physiology and behaviour, aligning their respective processes and activity with the prevailing light–dark cycle and the animal's internal physiological demands. To provide such timing signals, SCN neurons vary their membrane excitability state, so that their RMPs are generally more depolarised during the day than at night. In some SCN neurons, action potential discharge patterns are in phase with the day–night RMP rhythm, firing at higher rates during the day than at night. In others, the daytime RMP becomes too depolarised for spiking, and the neurons enter a silent state of depolarisation blockade or generate 2–7 Hz DLAMOs during the afternoon, before traversing to the hypoexcited night state. These RMP and firing rate excursions produce a sinusoidal excitability waveform in the SCN that peaks during the day and troughs at night, sustaining a neuronal oscillation with a near 24-h period or wavelength (Fig. 1).

In most SCN neurons, the drive to peak excitation during the day and hypoexcitation at night results from the activity of an internal molecular clockwork, where perpetual daily oscillations in clock gene expression regulate intracellular signalling cascades, ion channel activity and neurotransmitter release. Despite our formidable knowledge of the cell-autonomous processes that cause daily oscillations in clock gene expression, our understanding of how the molecular clockwork interacts with the membrane to regulate excitability of SCN neurons is severely lacking. Feedback cues from the environment and internal physiology also signal to SCN neurons, adjusting the timing precision of their internal molecular clockwork. This raises an interesting conundrum, because to influence the activity of the clock these resetting cues must first signal through the plasma membrane (Fig. 2). The mechanisms involved in this electrical-genetic interaction remain elusive, but emerging evidence, both in mammals and Drosophila clocks, supports the concept that the plasma membrane is not merely the proximal target of the molecular clockwork, but its excitability is integral to the functioning of the clock (Nitabach *et al.,* 2002, 2006; Lundkvist & Block, 2005;

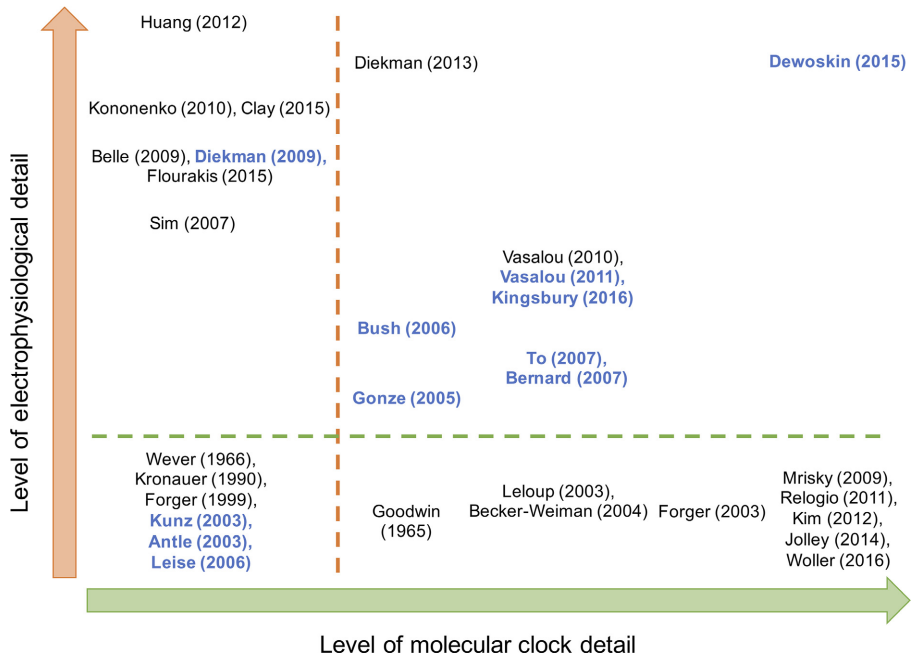

FIG. 6. Visual summary of the level of molecular clock and electrophysiological detail of 31 circadian models in the literature. Models below the green line are purely molecular, and models to the left of the orange line are purely electrophysiological. Models in the lower left quadrant are phenomenological (i.e., neither molecular nor electrophysiological), and models in the upper right quadrant have both molecular and electrophysiological components. Models in black font are single-cell models, and models in blue font are network models.

Lundkvist *et al.,* 2005; Wu *et al.,* 2008; Diekman *et al.,* 2013; Granados-Fuentes *et al.,* 2015), conceptualised here as the membrane clock (Fig. 2). An ingenious study in flies by Mizrak and colleagues established that the membrane clock can indeed feedback to impose time-of-day stamps onto the molecular clock transcriptome, acting as an internal zeitgeber (time-giver; Mizrak *et al.,* 2012). Alternatively, intercellular signals could also influence the activity of the molecular clock in manners that are independent of membrane excitability. For example, VIP could directly activate clock gene transcription through its effects on intracellular calcium and cAMP signalling (Akiyama *et al.,* 2001; Travnickova-Bendova *et al.,* 2002; Itri & Colwell, 2003; Irwin & Allen, 2010). Indeed, calcium entry through glutamatergic receptors activation could also have similar direct modulating effects on clock gene transcription alongside or independent of electrical excitation. Remarkably, therefore, the circadian clock functions through an autonomous and intricate genetic-electrical interplay which dynamically regulates, integrates and processes converging inputs at multiple cellular and network levels, while simultaneously broadcasting circadian signals across the brain and body.

Undeniably, neuronal rhythms are a widespread phenomenon, spanning across several brain regions and a wide range of frequency bands, from 0.05 to 600 Hz. In some of these structures, such as the hippocampus and cortex, these fast rhythms coexist alongside the much slower circadian oscillations. Interestingly, even in the SCN, faster ultradian and beta/gamma rhythms are found embedded within the slower circadian cycle. Uncovering the relationship between these brain-wide neuronal oscillators is a daunting challenge, but a necessary task if we are to understand how the all-important timing in physiology and behaviour is dynamically shaped and organised at multiple timescales (see Fig. 3). Across the forebrain regions, slow rhythms are known to influence the amplitude of oscillations with higher frequencies, synchronise large spatial domains and temporally link neurons into assemblies. Thus, taking all this into account, circadian rhythms must therefore be studied in the context of other brain oscillations if we are to understand their roles in shaping faster global brain events. In support, despite the wide distribution of neuronal oscillators along the frequency spectrum, the frequencies of these oscillations form a linear progression on the natural logarithmic scale (Freeman *et al.,* 2000; Penttonen & Buzsaki, 2003), perhaps mathematically underscoring their brain-wide interconnection. In the context of circadian timing, it is therefore conceivable that neuronal oscillations in the SCN at the circadian, ultradian and faster timescales represent the critical 'middle ground', linking single neuron activity, at the microsecond and millisecond timescales of ion channel conductance, action potential firing and synaptic release, to circadian pattern generation in physiology and behaviour.

Indeed, as demonstrated across the neuroscience disciplines and beyond, mathematical modelling has become an indispensable companion for driving our hypotheses, guiding our experiments and clarifying our understanding. This alliance between the two fields will no doubt be central in our strive to unravel some of the idiosyncratic processes in brain operation, physiology and behaviour that otherwise would be impenetrable.

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Conflict of interest

The authors have no conflict of interests to declare.

Author contributions

MDCB conceived and wrote the physiological data section. COD conceived and wrote the computational modelling section. MDCB and COD edited the manuscript and approved the submission of the final version.

Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; APs, action potentials; AVP, arginine vasopressin; BK_{Ca}, large-conductance calcium-activated potassium channels; *Bmal1*, brain and muscle Arnt-like gene-1; BMAL1, brain and muscle Arnt-like protein-1; $[Ca^{2+}]_i$, intracellular calcium; cAMP, cyclic adenosine monophosphate; CLOCK/BMAL1, CLOCK and BMAL1 heterodimer; *Clock*, circadian locomotor output cycles Kaput gene; CLOCK, circadian locomotor output cycles Kaput protein; COiCaSR, clock-operated intracellular calcium store release; *Cry1*, *cryptochrome 1* gene; CRY1, cryptochrome 1 protein; *Cry2*, *cryptochrome 2* gene; CRY2, cryptochrome 2 protein; DCM, dynamic causal modelling; DLAMOs, depolarised low-amplitude membrane oscillations; EEG, electroencephalogram; EGFP, enhanced green fluorescent protein; FDR, fast delayed rectifier; GABA, gamma-aminobutyric acid; g_{Ca}, calcium conductance; GFAP, glial fibrillary acidic protein; geniculohypothalamic tract; g_K, potassium conductance; GRP, gastrin releasing peptide; I_{Ca}, calcium current; IGL, intergeniculate leaflet; I_K, potassium current; I_L, passive 'leak' current; I_{Na}, sodium current; K2P, two-tandem pore domain potassium channels; LAMOs, low-amplitude membrane oscillations; LD, light–dark cycle; LL, light–light cycle or constant light conditions; NACLN, voltage-insensitive nonselective cation channel; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; ODEs, ordinary differential equations; PDE, partial differential equation; PER/CRY, PER/CRY proteins heterodimer; *Per1*, *Period1* gene; PER1, Period1 protein; *Per2*, *Period2* gene; PER2, Period2 protein; PK2, prokineticin 2; PKR2, receptor for PK2; *Rev-erbα*, gene; REV-ERBα, protein; RHT, retino-hypothalamic tract; RMP, resting membrane potential; RyR1, ryanodine receptor type 1; RyR2, ryanodine receptor type 2; RyRs, ryanodine receptors; SCN, suprachiasmatic nuclei; SK_{Ca}, small-conductance calcium-activated potassium channels; SVC, subthreshold voltage-gated cation channels; TGFα, transforming growth factor α; TTFL, transcription-translation feedback loop; TTX, tetrodotoxin; V1a/b, receptors for AVP; VGCCs, voltage-gated calcium channels; VIP, vasoactive intestinal polypeptide; VPAC2, receptor for VIP; ZT, zeitgeber time (time-giver).

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