Orexin and Circadian Influences in Sleep and Psychiatric Disorders: A Review of Experimental and Computational Modelling Studies

Link to publication record in Ulster University Research Portal

Document Version
Publisher's PDF, also known as Version of record

Orexin and Circadian Influences in Sleep and Psychiatric Disorders: A Review of Experimental and Computational Modelling Studies

Alok Joshi, Mino D.C. Belle, KongFatt Wong-Lin and Hugh D. Piggins

Abstract Psychiatric disorders such as unipolar depression have complex pathologies, which include disruptions in circadian and sleep-wake cycles. At the neurochemical level, psychiatric diseases can also be accompanied by changes in neuromodulator systems such as orexin/hypocretin and the monoamines. Indeed, for decades the monoamine hypothesis of depression has been instrumental in driving discoveries and developments of antidepressant drugs. Recent preclinical and clinical advancement strongly suggests that neuropeptides such as orexin can play an important part in the pathophysiology of depression. Due to the complexity and extensive connectedness of neurobiological systems, understanding the biological causes and mechanisms of psychiatric disorders present major research challenges. In this chapter, we review experimental and computational studies investigating the complex relationship between orexinergic, monoaminergic, circadian oscillators, and sleep-wake neural circuitry. Our main aim is to understand how these physiological systems interact and how alteration in any of these factors can contribute to the behaviours commonly observed in depressive patients. Further, we examine how modelling across different levels of neurobiological organization enables insight into these interactions. We propose that a multiscale systems approach is necessary to understand the complex neurobiological systems whose dysfunctions are the underlying causes of psychiatric disorders. Such an approach could illuminate future treatments.

A. Joshi (✉) · M.D.C. Belle · H.D. Piggins
Faculty of Life Sciences, University of Manchester, Manchester, M13 9PT, UK
e-mail: alok.joshi@manchester.ac.uk

K. Wong-Lin
Intelligent Systems Research Centre, University of Ulster, Magee Campus,
Derry, BT48 7JL, Northern Ireland, UK

1 Introduction

Psychiatric disorders such as depression, schizophrenia, and bipolar disorder are multifaceted illnesses that present our society with significant challenges and burdens. In 2010, the Global Burden of Disease Study has rated mental and substance use disorders as the principal causes of global health burden (Whiteford et al. 2013). The trend is likely to continue and by 2030, it is estimated that among brain diseases, unipolar depressive disorder will be the largest cause of disability (Mathers and Loncar 2006). Such forecasts demonstrate the perniciousness of these disorders and also raise questions concerning current treatment strategies.

Many factors including neuromodulators and circadian rhythms as well as the patterns and quality of sleep contribute to the pathophysiology of psychiatric disorders (Germain and Kupfer 2008; Pandi-Perumal et al. 2009; Hasler 2010; Murray and Harvey 2010; Wulff et al. 2012). Individually, these factors have been discussed and reviewed extensively (Delgado 2000; Tsuno et al. 2005; Germain and Kupfer 2008; Murray and Harvey 2010; Wulff et al. 2012), while their potential interactions have received relatively little attention (Fig. 1). A comprehensive consideration of these factors and their interactions for psychiatric disorders is beyond the scope of this review. Therefore, the focus of this chapter will be on understanding how monoamines, orexin (also called hypocretin), sleep, and circadian oscillator(s) mutually interact, and how the disruption in one or more of these factors might contribute to the certain behavioural phenotypes that are altered in unipolar depressive disorder. In some cases, the relationships with other psychiatric disorders (schizophrenia or bipolar disorder) are also briefly discussed. While considering these interactions, emphasis is placed on the circadian system, especially the way it regulates the activity of specific neuromodulators and behavioural states, and how its disruption influences these interactions to potentially contribute to specific symptoms such as mood and sleep problems commonly observed in psychiatric disorders.

The organization of the chapter is as follows. The role of monoamines and orexin in psychiatric disorders are first discussed, and then the role of orexin along with other neuromodulators in the regulation of the sleep-wake cycle will be discussed. This is followed by a discussion of the regulatory functions of the main circadian pacemaker in the suprachiasmatic nuclei (SCN) which coordinates and drives daily activity in other semi-autonomous oscillators in the brain (such as lateral habenula, LHb) and controls circadian timing in some neuromodulatory systems (orexin, monoamines) and sleep. Then a computational modelling perspective will be presented. Finally, there will be a discussion on key unanswered questions and identification of future research directions.
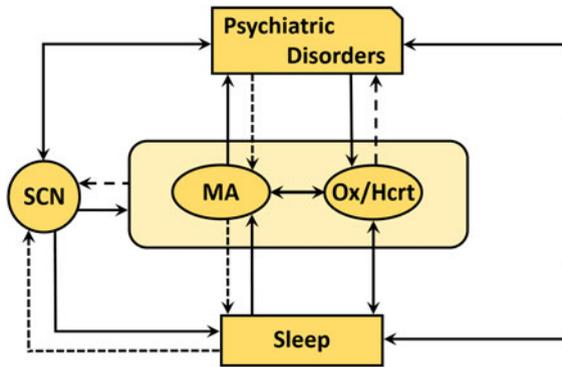
Fig. 1 Complex interactions of the master circadian oscillator in the suprachiasmatic nuclei (*SCN*), neuromodulators (e.g. orexin/hypocretin Ox/Hcrt; monoamines *MA*), sleep and psychiatric disorders. *Circle:* master circadian oscillator; *Oval:* neuromodulators; *Snip single corner rectangle:* psychiatric disorders; *Rectangle:* sleep; *Solid arrows:* known interactions; *Dashed arrows:* tentative interactions

2 Neuromodulators and Psychiatric Disorders

Results from many studies have indicated that altered circadian rhythms, disrupted sleep and abnormal basal levels of neuromodulators are associated with the clinical status of patients experiencing depression (Wehr et al. 1983; Ruhe et al. 2007; Wirz-Justice 2008; Germain and Kupfer 2008). Many of these characteristics are captured by the monoamine imbalance hypothesis which posits that perturbation in the basal levels of monoamines such as serotonin (5-HT), norepinephrine/noradrenaline (NE/NA), and dopamine (DA) can trigger depression (Nemeroff 1998). These monoamines are mainly synthesized at different brain regions. For example, 5-HT is synthesized in the raphe nuclei, NE in the locus coeruleus (LC), and DA in the substantia nigra and ventral tegmental area (VTA) (Grzanna and Molliver 1980; Park et al. 1999; Anzalone et al. 2012). These monoamine producing neurons project to many parts of the brain and are involved in the regulation of a wide range of behaviours (Leibowitz and Shor-Posner 1986; Cools et al. 2008; Aston-Jones et al. 2000; Bromberg-Martin et al. 2010). To understand how alteration in monoaminergic levels influences depression, many studies have focused on the expression and functionality of the monoaminergic receptors and transporters at the source and projection sites (Klimek et al. 1997; Rajkowska 2000; Arango et al. 2001; Boldrini et al. 2005). For example, depressed subjects have decreased 5-HT transporter, altered 5-HT$_{1A/2A}$ binding sites, and lower level of plasma tryptophan and metabolites (Quintana 1992; Owens and Nemeroff 1994; Malison et al. 1998; Drevets et al. 1999; Mintun et al. 2004). In the case of NE, altered adrenoreceptor (α_2) densities and lower NE levels have been observed in brain sites innervated by NE neurons, including the cortex (Ordway et al. 2003; Valdizán et al. 2010; Lanni et al. 2009; Moret and Briley 2011). Such changes may arise from reduced NE innervation, reduction in NE transporter

activity in NE-containing terminals, or by a combination of both (Klimek et al. 1997). For DA, lower transporter binding potential (a correlate of receptor density) in striatum is reported in depressed patients (Meyer et al. 2001). Similar findings were also observed in depressed patients with anhedonia symptoms (Sarchiapone et al. 2006). However, there are inconsistencies between different studies (Laasonen-Balk et al. 1999). Similarly, investigations have also measured DA metabolites in the CSF, but these results are not necessarily conclusive (Dunlop and Nemeroff 2007).

Despite the inconsistencies, such findings have led to the development of pharmaceutical treatments of unipolar depression. Many antidepressant compounds are designed to increase monoamine levels in the central nervous system (CNS). The strategy for drug treatments for other disorders can vary since the symptomatology can be diverse and dynamic (Bowden 2005; Walderhaug et al. 2011). Current research focuses on other novel treatment options include the exploration of peptidergic ligands. Clinical and preclinical studies are suggestive of the roles of neuropeptide mechanisms (e.g. orexin, vasopressin, galanin, corticotropin-releasing hormone, neuropeptide Y, relaxin-3 and substance P) in the pathophysiology of psychiatric disorders, including depression (Den Boer 2006; Madaan and Wilson 2009; Nollet and Leman 2013). Indeed, emerging drug targets for the treatment of psychiatric disorders are compounds that signal via neuropeptide receptors (Fang et al. 2014; Smith et al. 2014).

Among the neuropeptides potentially involved in the symptomatology of psychiatric disorders are the orexins (Ox; also called the hypocretins or hcrt). These neuropeptides occur in two forms, Ox-A and Ox-B, and are produced by neurons in the lateral, perifornical and dorsomedial areas of the hypothalamus (Sakurai et al. 1998; de Lecea et al. 1998). These Ox-containing neurons send projections to many brain regions (Peyron et al. 1998), including key regions that regulate arousal and motivational states such as the dorsal raphe nucleus (DRN), LC, arcuate nucleus, VTA, tuberomammillary nucleus (TMN), basal forebrain (BF) and laterodorsal and pedunculopontine tegmental nucleus (LDT/PPT) (Tsujino and Sakurai 2009). Through these and other neural connections, Ox play key roles in the regulation of important behaviours and physiological functions such as sleep-wake cycle, energy homeostasis, addiction, endocrine function, reward seeking, and emotional behaviour (de Lecea et al. 2006; Sakurai 2006, 2007, 2010, 2014; Tsujino and Sakurai 2009; Aston-Jones et al. 2009; López et al. 2010). Interestingly, many of these are disrupted in depression (Drevets 2001), suggesting that insights into Ox signaling may lead to a better understanding of the biological basis of depression. Indeed, in the last few years, there have been many studies in humans and animals investigating the role of Ox in depression as well as in other psychiatric disorders.

For example, it has been known that Ox levels can exhibit circadian variation and depressed patients manifest lower amplitude circadian variation in Ox levels in the cerebrospinal fluid (CSF) than do control individuals. Treatment with sertraline (a selective serotonin reuptake inhibitor (SSRI) anti-depressant) decreased mean Ox levels, suggesting that elevated Ox signaling contributes to the depressive

symptoms (Salomon et al. 2003). Such a putative interaction appears complex since other studies have reported that following attempted suicide the CSF Ox levels are decreased (Brundin et al. 2007a, b). In a later follow-up study (6–12 months after the attempt), CSF Ox levels among suicide survivors were relatively high compared to those measured immediately following suicide attempt (Brundin et al. 2009). In another investigation, Ox levels were reportedly unaltered in manic, control and depressed patients (Schmidt et al. 2010). Thus the effects of Ox in depression in humans remain inconclusive.

The relationship between Ox and depression has been also explored in animal models. For example, in the Flinders Sensitive Line (FSL), a rat genetic model of depression in which the animals are more susceptible to cholinergic agonists, the number of Ox neurons are higher than in control rats (Overstreet 1986; Overstreet et al. 2005; Mikrouli et al. 2011). Similarly, a 20 % increase in the number of detectable Ox neurons in lateral hypothalamus area was recently reported in a rodent model where high dosage of corticosterone treatment results in depressive like symptoms (Jalewa et al. 2014b). These findings suggest that during depression, either the number of Ox neurons increases or Ox synthesis increases, such that Ox-containing neurons are more readily available in the hypothalamus. In support for this interpretation, central infusion of Ox stimulates the hypothalamic–pituitary–adrenal (HPA) axis (Kuru et al. 2000), and hyperactivity of the HPA axis is often associated with depression (Vreeburg et al. 2009). Interestingly, attenuating Ox signaling in rodents through treatment with the Ox receptor antagonist almorexant improves HPA functioning and decreases behavioural measures of depression (Nollet et al. 2012). In contrast, exogenous treatments with Ox-A can have anti-depressant properties (Ito et al. 2008), suggesting that reduced Ox levels are associated with depression.

Ox is also potentially involved in other psychiatric disorders. For example, Ox signaling influences attentional and cognitive activities and has been linked with schizophrenia (Deutch et al. 2005; Lambe et al. 2007; Fukunaka et al. 2007; Poirier et al. 2010). Interestingly, higher plasma Ox levels are associated with improved symptoms in schizophrenia (Chien et al. 2015). There is also robust evidence indicating that a reduction in Ox neurons can lead to narcolepsy (Lin et al. 1999; Chemelli et al. 1999; Peyron et al. 2000). Since psychiatric patients frequently develop sleep disorders, this raises the possibility that changes in Ox signaling contributes to such arousal and wake-rest disruptions. This is explored in the next section.

3 Neuromodulators and Sleep

In mice, direct injection of Ox-A into the brain promotes wakefulness and suppresses non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Mieda et al. 2011), while similar treatment with a dual Ox_1/Ox_2 receptor antagonist promotes sleep and reduces locomotion (Mang et al. 2012). Thus, the activity of Ox neurons and Ox release varies across the sleep-wake cycle. Indeed, during the wake

state, Ox neurons in rodents are very active (Lee et al. 2005b; Marston et al. 2008; Estabrooke et al. 2001), coinciding with the time when Ox release is maximal (Deboer et al. 2004). As noted earlier, Ox neurons innervate arousal-promoting nuclei in the pons, midbrain, posterior hypothalamus and forebrain, and since the main action of Ox is excitatory, it is interpreted that Ox activates neurons in these nuclei to drive wakefulness. Such neurons are major sources of acetylcholine, histamine, serotonin, and norepinephrine, all of which are known to contribute to arousal states. Indeed, the activity of these neurochemically identified neurons is higher during wakefulness than in sleep. Thus, during wakefulness, the outputs of arousal-promoting neurons act to inhibit the activity of NREM and REM promoting neurons in ventrolateral preoptic nucleus (VLPO) and LDT/PPT, respectively, and relay excitatory signals to the thalamus and cortical neurons (Saper et al. 2001; España and Scammell 2011).

During NREM sleep, neurons of the preoptic areas are activated, and these neurons act to inhibit the wake and REM-promoting neurons elsewhere in the brain. Thus, during this time, the firing in monoaminergic neurons decreases significantly and ceases completely in the cholinergic and Ox neurons (Saper et al. 2001; España and Scammell 2011). In addition to the preoptic neurons, interneurons (mainly GABAergic) in some of the arousal areas (LHA and BF) are also active during NREM phase and contribute in conveying inhibitory signals to the cortex to promote slow wave sleep (Manns et al. 2000; Hassani et al. 2009, 2010).

REM sleep occurs during the transition from NREM to waking states (Saper et al. 2001). Hallmark features of REM sleep include cortical activation and loss of muscle tone. Interestingly, during REM sleep, Ox neurons are not completely silenced but instead contribute to the phasic components of this brain state (Torterolo and Chase 2014). By contrast, during REM, cholinergic and VLPO neurons show high firing rate, while monoaminergic neurons cease firing (España and Scammell 2011). Thus an imbalance between cholinergic and monoaminergic discharge activity may contribute to the disruption between REM and NREM sleep which is very common among depression sufferers. Moreover, an imbalance between Ox and monoaminergic activity is believed to be a key factor in narcolepsy and depression (Brown et al. 2001; Feng et al. 2008).

These interpretations can be better understood by considering the two-process model of the dynamic regulation of sleep-wake cycle (Borbély 1982; Daan et al. 1984). It is widely believed that this regulation is achieved via two separate biological processes where process **S** is responsible for sleep homeostasis, and process **C** controls the circadian timing (via the circadian clock) (Fig. 2). Accordingly, the increase in sleep pressure that occurs during wakefulness subsequently declines during sleep. Studies have linked this pressure with extracellular adenosine levels (Sims et al. 2013; Huang et al. 2014). Adenosine forms from the degradation of adenine nucleotides, and during wakefulness its levels are believed to be increased in the BF and cortical regions (Huang et al. 2014). Thus, depending upon the adenosine concentration, process **S** sends timing signals to process **C** and regulates the sleep-wake cycle. So, the circadian clock not just controls the timing of process **S** but also interacts with various sleep stages, which may well decide the recovery
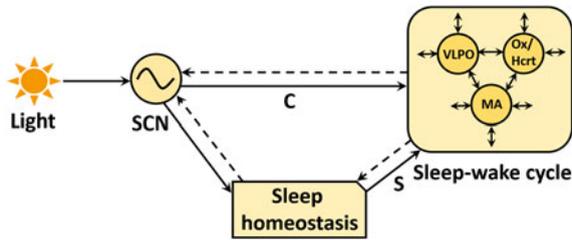
Fig. 2 A two-process model of sleep. The circadian clock in the SCN receives light inputs and sends the timing signals (**C**) to regions of the brain involved in sleep-wake (S-W) cycle and to a conceptual sleep homeostasis process which further regulates the balance between sleep and wake state. The S-W cycle is controlled by the complex interactions between sleep (ventrolateral preoptic nucleus VLPO) and wake promoting neurons (MA, Ox). *Circle*: circadian oscillator, sleep and wake promoting areas; *Snip single corner rectangle*: sleep homeostasis; *Solid and dashed arrows* as in Fig. 1 (Borbély 1982; Daan et al. 1984; Dijk and Lockley 2002)

pattern in instances of sleep deprivation. Interestingly, a study shows that activity of neurons in the brain's master circadian clock in the suprachiasmatic nuclei (SCN) is higher during the REM and wake states, and relatively lower during the NREM state (Deboer et al. 2003). There is further evidence that suggests that mutation, polymorphism or deletion of some of the clock genes disrupt sleep homeostasis and response to the sleep deprivation (Naylor et al. 2000; Toh et al. 2001; Laposky et al. 2005; Dijk and Lockley 2002). However, how changes in sleep-wake patterns affect the molecular mechanism of the clock still remains unknown (Deboer et al. 2003).

In the next section, we shall discuss how the circadian pacemaker in the SCN drives daily timing in different brain areas and regulates neuromodulator levels and sleep. We will also discuss how disruption of circadian clock timing is linked to specific symptoms commonly observed in psychiatric disorders.

4 Circadian Rhythms

Circadian rhythms are intrinsic near 24 h oscillations and pervade all aspects of physiology and behaviour. Neurons of the SCN contain the intracellular circadian clock of which the *Period* (*Per1-2*), *Cryptochrome* (*Cry1-2*), *Circadian Locomotor Output Cycles Kaput (CLOCK)* and *Brain and Muscle ARNT-like protein 1 (Bmal1)* genes and their protein products play important roles (Mohawk and Takahashi 2011). The synchronized activity of these autonomous cellular clocks enables the SCN as a whole to function as the master clock. In turn, the SCN receives information about environmental lighting directly from the retina, with daily variation in light entraining the SCN to the external world (Fig. 2). The SCN output then communicates these integrated timekeeping signals to the rest of the brain and body to control daily rhythms in sleeping and waking, metabolism, cognition, and mood (Piggins and Guilding 2011).

Intriguingly, as noted earlier, in many psychiatric conditions, alterations in sleeping and waking as well as mood are frequently present as part of the patients' symptoms, suggesting that SCN or SCN-regulated processes are disrupted in such disorders (Wulff et al. 2010; Menet and Rosbash 2011; McCarthy and Welsh 2012; Schnell et al. 2014; Gonzalez 2014). Indeed, in mice, genetic alterations that affect components of the intracellular molecular clock are implicated as murine models of human psychiatric conditions (Landgraf et al. 2014). For example, the Δ19 mutation of the *clock* gene, results in a dysfunctional CLOCK protein and the mouse manifests >24 h rhythms or lacks circadian rhythms as well as hyperactivity and other hallmarks of mania (Vitaterna et al. 1994; McClung et al. 2005; Roybal et al. 2007; Sidor et al. 2015). Such a mutation directly affects the SCN clock, but since circadian clock genes are also expressed in other brain areas as well as peripheral tissues, local physiology can be affected in such regions and organs. In the case of the Δ19 clock mutant mouse, mania-like behaviours are attributable to dysfunction of dopamine neurons in the VTA. This appears to be due to changes in gene regulation normally under the control of CLOCK (Mukherjee et al. 2010). Another mutation that influences the stability of CRY proteins also lengthens the period of circadian rhythms, which is accompanied by changes in anxiety (Keers et al. 2012).

In humans, some mutations in clock genes are associated with the sleep-wake cycle. Of note, treatment of bipolar disorder can include lithium which exerts some of its actions via GSK-3beta, a key regulator of the intracellular molecular clock (Iitaka et al. 2005). Indeed, in animal studies, lithium lengthens the period of the molecular clock rhythms and locomotor behavior (Welsh and Moore-Ede 1990; Li et al. 2012).

In rodents the activity of Ox neurons is under SCN circadian control (Zhang et al. 2004), with higher activity occurring during the behaviourally-active circadian night (Estabrooke et al. 2001; Marston et al. 2008). At this phase, Ox release in the brain is also at maximal (Deboer et al. 2004). Experimental destruction of the SCN or exposure to constant light, which attenuates SCN output, abolishes circadian variation in CSF levels of Ox, indicating that the day-night activity profile of this key arousal-promoting neurochemical is under SCN output control. Interestingly, the phase of the SCN circadian clockwork is also sensitive to feedback actions of arousal-promoting stimuli, particularly during the behaviourally-inactive circadian day (Hughes and Piggins 2012). During the day, arousal-promoting stimuli activate Ox neurons (Estabrooke et al. 2001; Marston et al. 2008; Webb et al. 2008) and suppress the SCN's electrical activity (van Oosterhout et al. 2012). Indeed, in SCN brain slice preparations Ox not only suppresses the electrical activity of SCN neurons, but also potentiates the phase-shifting capacity of another neurochemical correlate of arousal, neuropeptide Y (Belle et al. 2014).

Hence, alterations in the SCN circadian clock as well as circadian regulation of the brain and behavioural states can result in symptoms seen in psychiatric conditions. Since Ox-containing neurons project widely across the brain (Peyron et al. 1998; Nambu et al. 1999), including structures of the neural circadian system (McGranaghan and Piggins 2001; Backberg et al. 2002), Ox released during states of arousal can influence circadian timing in SCN and extra-SCN brain sites (Fig. 3). This may be particularly important in psychiatric conditions when the pattern of
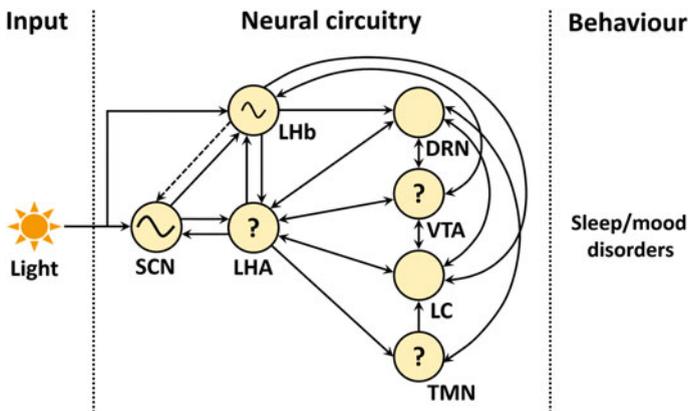
Fig. 3 Circadian clock, neuromodulators and their possible role in the etiology of sleep and mood disorders. Suprachiasmatic nuclei (SCN) with lateral habenula (LHb) receive the light inputs and regulate the activity of other brain areas that are important in S-W and mood regulation. SCN, LHb: master and semi-autonomous clocks. Lateral hypothalamus area (LHA), dorsal raphe nucleus (DRN), ventral tegmental area (VTA), locus coeruleus (LC), and tuberomamillary nucleus (TMN): major source of orexin/hypocretin, serotonin, dopamine, norepinephrine and histamine, respectively. '?': Either clock gene(s) are present in these areas (existence of intrinsic activity not yet confirmed) or their daily activity is indirectly regulated by the circadian clocks present in other brain regions (e.g. SCN and/or LHb). *Circle*: circadian oscillators (SCN, LHb), LHA and monoaminergic areas; *Note*: non-photic inputs are not shown (Jones and Moore 1977; Herkenham and Nauta 1979; Segal 1979; Deutch et al. 1986; Kalen et al. 1988; Ericson et al.1989; Herkenham and Nauta 1993; Peyron et al. 1998; Nambu et al. 1999; Abrahamson et al. 2001; Yoshida et al. 2001; Kim et al. 2004; Mileykovskiy et al. 2005; Lee et al. 2005a; McClung et al. 2005; Hattar et al. 2006; Guilding and Piggins 2007; Vertes and Linley 2008; Omelchenko et al. 2009; Tsujino and Sakurai, 2009; Schwartz et al. 2011; Goncalves et al. 2012; Watabe-Uchida et al. 2012; Stamatakis et al. 2013; Belle et al. 2014; Dorocic et al. 2014; Proulx et al. 2014; Root et al. 2014; Sakhi et al. 2014; Yu et al. 2014; Ogawa et al. 2014)

sleeping and waking is severely disturbed. Incorporating such knowledge when considering the treatments and the timing of treatments, therefore, has considerable therapeutic potential.

Thus, mutual interactions between circadian clock, neuromodulators and sleep are likely to be important in understanding the biological mechanisms of some aspects of psychiatric disorders. However, the behaviours due to these interactions are not intuitive. For example, 5-HT neurons in the DRN receive inputs from other monoaminergic neurons including the NE-containing neurons of the LC, histamine-containing neurons from TMN, as do DA neurons of the VTA (Kalen et al. 1988; Lee et al. 2005a; Dorocic et al. 2014; Ogawa et al. 2014). Additionally, the activities of these neuromodulators are also regulated by their auto-receptors. Thus, it is very difficult to assess the causal relationship (between activities or firing rate) among the different brain areas to establish precisely how these changes can cause or affect the severity of a symptom.

A promising approach towards assessing and understanding such complex interacting systems is to develop, simulate and analyze computational models. Some

initial cognitive computational models have focused on improving the diagnosis of psychiatric disorders (Siegle 1999; Siegle and Hasselmo 2002). More recent cognitive computational models have focused on decision-making, reward and reinforcement learning aspects, e.g. learned helplessness and anhedonia, which are the core symptoms in depression (Dayan and Huys 2008; Gradin et al. 2011; Huys et al. 2013). However, these models are based on high-level abstractions and hence do not readily illuminate the underlying biological mechanisms underpinning the disorders. Moreover, there is a lack of modelling on the interactions between Ox and other neuromodulators, and their effects on sleep and depression. This is not surprising as substantial modelling and analysis work was more focused on associating Ox with the sleep-wake cycle, and in particular, its role in narcolepsy [e.g. (Behn et al. 2010)]. In the next section, we will briefly review some biologically based computational modelling studies on Ox, monoamines, circadian rhythms, and sleep-wake dynamics.

5   Neural Computational Models

The mathematical modelling and analysis of sleep-wake dynamics and circadian rhythms have a relatively long history, primarily due to the availability of behavioural and physiological (e.g. temperature and neuroendocrine) data (Czeisler 1978; Czeisler et al. 1980; Daan et al. 1984; Kawato et al. 1982; Kronauer et al. 1982, 1983; Strogatz and Carpenter 1986; Strogatz 1987; Winfree 1983). All these models address the sleep-wake dynamics and various autonomic circadian rhythms. There is a considerable similarity among these models (Kronauer et al. 1982; Kronauer et al. 1983), which typically consist of homogeneous neuronal populations, or coarse-grained population-averaged (firing-rate) type models (Wilson and Cowan 1972). The simplicity of the models allows tractability in the mathematical analyses and provides conceptual insights.

As various types of biological data become available, models of circadian rhythms become more physiologically detailed. At the molecular, genetic and protein levels, biochemical reactions and feedback loops are modelled to understand their regulations on the intrinsic circadian rhythms and their perturbations (Goldbeter 1995; Leloup and Goldbeter 2003; Forger and Peskin 2003). Physiologically, more realistic neuronal models of sleep-wake regulation have also begun, building on previously more abstract mathematical models (Behn et al. 2007; Phillips and Robinson 2007; Booth and Behn 2014). These models are typically considered at a single level of biological details.

At the neuronal level, a biophysical conductance-based model of the SCN neurons has successfully incorporated the available neuronal and synaptic properties in the SCN and can mimic the neuronal firing patterns, which are consistent with experiments (Sim and Forger 2007). Similar biophysical models for Ox neurons has also been developed with the minimal set of currents (Postnova et al. 2009; Carter et al. 2012) and model parameters were based on other neuronal types (Williams and Behn 2011). Despite the assumptions, such models could account for

some aspects of sleep-wake transitions (Postnova et al. 2009), and the dynamical effects of Ox and dynorphin, a colocalized neuropeptide, on the Ox neurons (Williams and Behn 2011). In Carter et al. (2012), a more biophysical two-compartmental model of Ox neuron was also developed.

Neurocomputational models at the microcircuit level may offer a way to investigate heterogeneity effects and emergent properties, which are not feasible at the single neuronal modelling level. For example, Postnova et al. (2009) incorporated local glutamatergic neurons to provide local feedback to the Ox neurons to understand homeostasis in sleep-wake transitions. Then, Patriarca et al. (2012) extended this model into a multi-neuron model and demonstrated that sufficient diversity in the synapses is needed to provide efficient functioning of the homeostasis regulation of the sleep-wake cycle. In Gonze et al. (2005) the model incorporated coupling among 10,000 circadian oscillators and found that spontaneous synchronization is achieved through the "mean-field" coupling and the population can be entrained with light pulses. In Wong-Lin et al. (2012), a microcircuit model of the DRN with non-5-HT GABAergic neurons was proposed to link from single neuronal spiking behaviours of 5-HT and local non-5-HT neurons in the DRN to phasic neuronal activity observed in behaving animals. The microcircuit DRN model suggested inputs via inhibitory neurons, and predicted low frequency oscillations in the network, which is clearly emergent network behaviour.

To understand the overall behaviour of a system as complex as that shown in Fig. 3, one would need to extend beyond microcircuit modelling levels, and towards larger circuit models that include the interactions of multiple brain regions (Sorooshyari et al. 2015). For example, Behn et al. (2007) modelled the interactions among the sleep active (VLPO), wake active (LC, DR, TMN) and REM active (LDT/PPT) neural populations. The model could capture some of the features of mouse the sleep-wake behaviour (such as short-term awakening), and also predicts the mechanism for state transitions. Subsequent modelling studies showed that Ox could play an important part in the sustenance and stabilization of prolonged episodes of wake and sleep (Behn et al. 2008; Fulcher et al. 2014). Similarly, the role of Ox is also analyzed for other large-scale modelling work that reasonably reproduce sleep-wake timings (under normal and sleep deprived conditions), circadian influence on total sleep time, and rapid transition between sleep and wake states with the loss of Ox (Rempe et al. 2010).

Recently, there has been considerable interest in more focused modelling of Ox system's interactions with that of the monoamines (Joshi et al. 2011; Carter et al. 2012; Jalewa et al. 2014a). A common aim of these studies is to understand the possible roles of such interactions in sleep and depression (Joshi et al. 2011; Carter et al. 2012; Jalewa et al. 2014a; Mosqueiro et al. 2014). In one of these studies, the excitability of LC neurons is shown to be important for Ox-mediated transition in sleep-to-wake transition (Carter et al. 2012). In a different study, a mathematical neural circuit model with direct interactions between the DRN and LHA is developed (Joshi et al. 2011). The model's novel input-output functions for the DRN and LHA areas are derived from the relationship between the neural firing rate in that area and neuromodulator concentration level, which can be obtained directly from

experiments. In addition, the dynamics of the release and uptake of the neuromodulators can, in principle, also be measured from experiments, e.g. voltammetry.

Even more complex models have been studied, where the models include not just across-region interactions, but also interactions with other local interneurons. For example, in Mosqueiro et al. (2014), inhibitory GABAergic interneurons are used to investigate the regulation of NE-producing LC neurons by Ox, in which the GABAergic neurons provide an indirect inhibitory connection from Ox to LC. This modelling work shows that the relatively fast GABA$_A$-mediated synapses are not sufficient to regulate LC activity. Similarly, the model in Jalewa et al. (2014a) has included more explicit interneurons, and for the first time, autoreceptors were included for the LHA-DRN interaction. More importantly, indirect connections are also considered in this model. The model demonstrates that LHA-DRN interactions are more stable if the indirect connections from 5-HT to GABAergic neurons in the LHA are strongly excitatory. Furthermore, it is found that faster 5-HT (e.g. via the 3A) receptor mediated timescales can quickly reset the Ox neuronal activities to baseline firing rate right after phasic 5-HT activation. Further, Kumar et al. (2012) have developed a mathematical model of REM-NREM dynamics that includes local GABAergic neurons, revealing the sensitive control of Ox on REM dynamics.

Taken together, these modeling studies have furthered our understanding of the relationship between Ox and the monoamines, and their roles in sleep-wake dynamics, providing mechanistic links to mood, cognition and psychiatric disorder. Despite the progress, integrated computational models that can link from cellular to behavioural levels have yet to be developed. Having such models would be of tremendous help in guiding future experiments across various levels.

6   Discussion

Many people worldwide suffer from psychiatric disorders. Depression is one psychiatric disorder with complex etiology and heterogeneous symptoms (Krishnan and Nestler 2008). Sleep anomalies and altered circadian rhythms are prevalent in depression (Germain and Kupfer 2008; Pandi-Perumal et al. 2009). Monoamine oxidase inhibitors (MAOI) are used for the clinical treatment of this atypical disorder (Thase et al. 1995) and are now augmented by drugs that target neuropeptide receptors, thought to be important in the etiology of depression (Saar et al. 2013; Nollet and Leman 2013; Yeoh et al. 2014).

In this chapter, we have discussed how Ox can interact with monoamines, circadian oscillators (e.g. SCN), and sleep wake-cycle. We raised some key issues, identified some of the unknown connections and attempted to understand how anomaly in one of the system can influence their complex interactions, which may contribute to certain behaviours that are common in psychiatric disorders.

Ox is a key neuropeptide which plays important roles in the regulation of a wide range of behaviours. Interestingly, Ox levels were inconsistent in different preclinical and clinical studies. There can be many reasons for such inconsistencies.

For example, Ox levels are regulated by the circadian clock and if not sampled at the same time in each study, considerable interstudy differences could emerge. Indeed, one investigation showed that depressed patients have dampened CSF Ox rhythms (Salomon et al. 2003). Similarly, circadian variation in serum serotonin and metabolites is also reported in depression (Pietraszek et al. 1991). Not surprisingly, there are other factors that may also contribute to inconsistency in measured brain neuromodulator levels. Some of them include heterogeneity among the animals (e.g. mice, rats), experimental protocols, small sample size and methods for measuring the neuromodulator levels (e.g. voltammetry, high-performance liquid chromatography or radioimmunoassay).

Another important issue is to conside whether Ox and other neuromodulator levels are regulated reciprocally. The last few years have witnessed a surge of interest in understanding Ox interactions with monoamines as these interactions can play important roles in the regulation of cognitive functions altered in many psychiatric disorders. Ox interaction with DA neurons may contribute to the better understanding of sleep related problems reported in schizophrenia, as anti-dopaminergic drugs actively lower the Ox CSF levels and promotes the NREM sleep in schizophrenics (Dalal et al. 2003). Also co-release of Ox with dynorphin in the VTA is important in motivational and reward-related behaviours (Muschamp et al. 2014) which are known to be disrupted in depression and schizophrenia. Similarly, knowledge of the interaction among Ox and serotonergic neurons is necessary for the better understanding of depression, as higher Ox levels in the hypothalamus are reported in a clomipramine (SSRI) induced rat model of depression (Feng et al. 2008). In some respects, there is much in common in these Ox-monoamine interactions. All these neuromodulators are active during arousal, and are also involved in some of the cognitive functions. The other similarity between Ox and other neuromodulators is the way Ox connects with them; interestingly Ox shares an excitatory-inhibitory feedback loop circuitry with these neuromodulators (e.g. serotonin, norepinephrine and dopamine). For example, Ox depolarizes these monoamine- containing neurons and conversely these neuromodulators can hyperpolarize Ox neurons in the LHA. Recently, experimental and modeling studies have contributed towards the better understanding of such interactions (Carter et al. 2012; Schone et al. 2014; Jalewa et al. 2014a). However, mutual interaction of all these arousal areas is neglected in the literature. This is because mutual interactions among the monoaminergic neurons add another layer of complexity, and practical implementation of these connections remains a considerable challenge.

Other than these complex interactions, Ox neurons also receive daily timing information from the SCN, and play a key role in the regulation of REM sleep (Kantor et al. 2009). However, the exact pathway via which SCN regulates Ox neurons and REM sleep is not known. One obvious possibility is that SCN and sleep homeostasis processes interact with sleep-wake states in accordance with the two-process model (Fig. 2). The other possibility is that the SCN directly regulates the sleep-wake cycle, and Ox plays a dual role where it stabilizes the sleep-wake switch and also regulates the sleep homeostasis process (Postnova et al. 2009). The excitatory drive of Ox neurons during wakefulness is due in part to excitatory

feedback connections between Ox and glutamatergic neurons within the LHA. It is possible that synaptic efficacy of Ox neurons decreases due to their prolonged activity during wakefulness which is recovered during sleep.

Apart from Ox, the SCN clock can also influence the process of sleep home-ostasis as this is disrupted in clock mutant mice (Naylor et al. 2000). However the exact relationship between Ox and the sleep homeostasis process remains elusive. Further, recent evidence indicating that clock genes influence the activity of DA neurons adds another level of complexity (McClung et al. 2005). This brings us to a question, whether a disrupted clock can influence the level of Ox or monoamines, and if so then what is the neural pathway of this dysregulation. One possibility is that the master clock in SCN first desynchronizes other local clocks (LHb, par-aventricular nucleus) or the areas with clock genes. These areas then indirectly communicates with the other brain areas, affecting the electrical activities of their neurons (Fig. 3). On the other side, a change in the level of Ox or monoamines can alter circadian rhythms in other physiological activity, such as the profile in stress hormones and the HPA axis (Mazzocchi et al. 2001; Spinazzi et al. 2006; Ziolkowska et al. 2005).

Thus the role of Ox is not just limited to the regulation of the sleep-wake states but it is involved in the regulation of a wide range of behaviours and cognitive functions (Mahler et al. 2014). Most of these behaviours are determined by the complex interaction between subcortical and cortical areas (Jankowski and Sesack 2004; Onge et al. 2012; Pujara and Koenigs 2014). However, linking the neuronal activity with the observed behaviour is one of the greatest challenges in neuroscience.

To accomplish this difficult task, one important approach is to collate the experimental data and build computational models across multiple levels, from intracellular processes in individual neurons to network properties and behavioural states. For example, a concerted effort to systematically collect neurobiological data, such as electrophysiological properties of neurons, release-and-reuptake dynamics of the neuromodulators, and receptor-mediated currents at the target sites, would be vital towards developing biologically faithful computational models of neuromodulation. With such data available, an integrated model endowed with multiscales can be developed. The multiscale modelling approach would extract the essence at each scale or level and integrate this with processes happening at other scales or levels (Yamada and Forger 2010; Vasalou and Henson 2010; Qu et al. 2011; Dada and Mendes 2011). Such effort in developing a multiscale framework for neuromodulator systems, from intracellular biochemical reactions to behaviour, is currently undertaken by the authors—(Eckhoff et al. 2009, 2011; Wong-Lin et al. 2012; Wang and Wong-Lin 2013; Laviale et al. 2013; Nakamura and Wong-Lin 2014; Flower and Wong-Lin 2014; Cullen and Wong-Lin 2014). With the avail-ability of such multiscale models, one can rapidly test hypothesis, and can make model predictions that can be verified by future experiments. Thus, computational models with pharmacological, imaging and optogenetic approaches can improve our understanding of the underlying neural mechanism(s) responsible for specific symptoms that are common in psychiatric disorders.

In summary, this chapter reviews studies related to Ox, monoamines, and circadian processes, and highlights some of their roles in psychiatric disorders. Further, we suggest the need to develop an integrated multiscale computational modelling framework that is based on systematic collection of experimental data. This will improve our understanding of how disruption in heterogeneous and highly connected neurochemically distinct neuronal populations and the circadian system contribute to symptoms in psychiatric conditions.

References

Abrahamson E, Leak R, Moore R (2001) The suprachiasmatic nucleus projects to posterior hypothalamic arousal systems. Neuroreport 12:435–440

Anzalone A, Lizardi-Ortiz JE, Ramos M, De Mei C, Hopf FW, Iaccarino C, Halbout B, Jacobsen J, Kinoshita C, Welter M (2012) Dual control of dopamine synthesis and release by presynaptic and postsynaptic dopamine D2 receptors. J Neurosci 32:9023–9034

Arango V, Underwood MD, Boldrini M, Tamir H, Kassir SA, Hsiung S-C, Chen JJ, Mann JJ (2001) Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. Neuropsychopharmacology 25:892–903

Aston-Jones G, Rajkowski J, Cohen J (2000) Locus coeruleus and regulation of behavioral flexibility and attention. Prog Brain Res 126:165–182

Aston-Jones G, Smith RJ, Moorman DE, Richardson KA (2009) Role of lateral hypothalamic orexin neurons in reward processing and addiction. Neuropharmacology 56:112–121

Backberg M, Hervieu G, Wilson S, Meister B (2002) Orexin receptor-1 (OX-R1) immunoreactivity in chemically identified neurons of the hypothalamus: focus on orexin targets involved in control of food and water intake. Eur J Neurosci 15:315–328

Behn CG, Brown EN, Scammell TE, Kopell NJ (2007) Mathematical model of network dynamics governing mouse sleep-wake behavior. J Neurophysiol 97:3828–3840

Behn CD, Kopell N, Brown EN, Mochizuki T, Scammell TE (2008) Delayed orexin signaling consolidates wakefulness and sleep: physiology and modeling. J Neurophysiol 99:3090–3103

Behn CGD, Klerman EB, Mochizuki T, Lin S-C, Scammell TE (2010) Abnormal sleep/wake dynamics in orexin knockout mice. Sleep 33:297

Belle MD, Hughes AT, Bechtold DA, Cunningham P, Pierucci M, Burdakov D, Piggins HD (2014) Acute suppressive and long-term phase modulation actions of orexin on the mammalian circadian clock. J Neurosci 34:3607–3621

Boldrini M, Underwood MD, Mann JJ, Arango V (2005) More tryptophan hydroxylase in the brainstem dorsal raphe nucleus in depressed suicides. Brain Res 1041:19–28

Booth V, Behn CGD (2014) Physiologically-based modeling of sleep–wake regulatory networks. Math Biosci 250:54–68

Borbély AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195–204

Bowden CL (2005) A different depression: clinical distinctions between bipolar and unipolar depression. J Affect Disord 84:117–125

Bromberg-Martin ES, Matsumoto M, Hikosaka O (2010) Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 68:815–834

Brown RE, Sergeeva O, Eriksson KS, Haas HL (2001) Orexin A excites serotonergic neurons in the dorsal raphe nucleus of the rat. Neuropharmacology 40:457–459

Brundin L, Bjorkqvist M, Petersen A, Traskman-Bendz L (2007a) Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder. Eur Neuropsychopharmacol 17:573–579

Brundin L, Petersen A, Bjorkqvist M, Traskman-Bendz L (2007b) Orexin and psychiatric symptoms in suicide attempters. J Affect Disord 100:259–263

Brundin L, Bjorkqvist M, Traskman-Bendz L, Petersen A (2009) Increased orexin levels in the cerebrospinal fluid the first year after a suicide attempt. J Affect Disord 113:179–182

Carter ME, Brill J, Bonnavion P, Huguenard JR, Huerta R, de Lecea L (2012) Mechanism for Hypocretin-mediated sleep-to-wake transitions. Proc Natl Acad Sci U S A 109:E2635–E2644

Chemelli RM, Willie JT, Sinton CM, Elmquist JK, Scammell T, Lee C, Richardson JA, Williams SC, Xiong Y, Kisanuki Y, Fitch TE, Nakazato M, Hammer RE, Saper CB, Yanagisawa M (1999) Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell 98:437–451

Chien Y-L, Liu C-M, Shan J-C, Lee H-J, Hsieh MH, Hwu H-G, Chiou L-C (2015) Elevated plasma orexin A levels in a subgroup of patients with schizophrenia associated with fewer negative and disorganized symptoms. Psychoneuroendocrinology 53:1–9

Cools R, Roberts AC, Robbins TW (2008) Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci 12:31–40

Cullen M, Wong-Lin K (2014) Analysis of a computational model of dopamine synthesis and release through perturbation. In: 2014 IEEE international conference on bioinformatics and biomedicine (BIBM), pp 1–7

Czeisler C (1978) Internal organization of temperature, sleep-wake, and neuroendocrine rhythms monitored in an environment free of time cues. Stanford University, Stanford

Czeisler CA, Weitzman E, Moore-Ede MC, Zimmerman JC, Knauer RS (1980) Human sleep: its duration and organization depend on its circadian phase. Science 210:1264–1267

Daan S, Beersma D, Borbély AA (1984) Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol-Regul Integr Comp Physiol 246:R161–R183

Dada JO, Mendes P (2011) Multi-scale modelling and simulation in systems biology. Integr Biol (Camb) 3:86–96

Dalal MA, Schuld A, Pollmacher T (2003) Lower CSF orexin A (hypocretin-1) levels in patients with schizophrenia treated with haloperidol compared to unmedicated subjects. Mol Psychiatry 8:836–837

Dayan P, Huys QJ (2008) Serotonin, inhibition, and negative mood. PLoS Comput Biol 4:e4

de Lecea L, Kilduff T, Peyron C, Gao X-B, Foye P, Danielson P, Fukuhara C, Battenberg E, Gautvik V, Bartlett FN (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci 95:322–327

de Lecea L, Jones BE, Boutrel B, Borgland SL, Nishino S, Bubser M, Dileone R (2006) Addiction and arousal: alternative roles of hypothalamic peptides. J Neurosci 26:10372–10375

Deboer T, Vansteensel MJ, Detari L, Meijer JH (2003) Sleep states alter activity of suprachiasmatic nucleus neurons. Nat Neurosci 6:1086–1090

Deboer T, Overeem S, Visser NA, Duindam H, Frolich M, Lammers GJ, Meijer JH (2004) Convergence of circadian and sleep regulatory mechanisms on hypocretin-1. Neuroscience 129:727–732

Delgado PL (2000) Depression: the case for a monoamine deficiency. J Clin Psychiatry 61(Suppl 6):7–11

Den Boer JA (2006) Looking beyond the monoamine hypothesis

Deutch AY, Goldstein M, Roth RH (1986) Activation of the locus coeruleus induced by selective stimulation of the ventral tegmental area. Brain Res 363:307–314

Deutch AY, Fadel J, Bubser M (2005) Dopamine-hypocretin/orexin interactions. In: Hypocretins. Springer, Berlin

Dijk D-J, Lockley SW (2002) Invited review: integration of human sleep-wake regulation and circadian rhythmicity. J Appl Physiol 92:852–862

Dorocic IP, Fürth D, Xuan Y, Johansson Y, Pozzi L, Silberberg G, Carlén M, Meletis K (2014) A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. Neuron 83:663–678

Drevets WC (2001) Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11:240–249

Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJ, Huang Y, Gautier C, Mathis C (1999) PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 46:1375–1387

Dunlop BW, Nemeroff CB (2007) The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 64:327–337

Eckhoff P, Wong-Lin KF, Holmes P (2009) Optimality and robustness of a biophysical decision-making model under norepinephrine modulation. J Neurosci 29:4301–4311

Eckhoff P, Wong-Lin K, Holmes P (2011) Dimension reduction and dynamics of a spiking neural network model for decision making under neuromodulation. SIAM J Appl Dyn Syst 10:148–188

Ericson H, Blomqvist A, Köhler C (1989) Brainstem afferents to the tuberomammillary nucleus in the rat brain with special reference to monoaminergic innervation. J Comp Neurol 281:169–192

España RA, Scammell TE (2011) Sleep neurobiology from a clinical perspective. Sleep 34:845

Estabrooke IV, McCarthy MT, Ko E, Chou TC, Chemelli RM, Yanagisawa M, Saper CB, Scammell TE (2001) Fos expression in orexin neurons varies with behavioral state. J Neurosci 21:1656–1662

Fang P, Min W, Sun Y, Guo L, Shi M, Bo P, Zhang Z (2014) The potential antidepressant and antidiabetic effects of galanin system. Pharmacol Biochem Behav 120:82–87

Feng P, Vurbic D, Wu Z, Hu Y, Strohl KP (2008) Changes in brain orexin levels in a rat model of depression induced by neonatal administration of clomipramine. J Psychopharmacol 22:784–791

Flower G, Wong-Lin K (2014) Reduced computational models of serotonin synthesis, release, and reuptake. IEEE Trans Biomed Eng 61:1054–1061

Forger DB, Peskin CS (2003) A detailed predictive model of the mammalian circadian clock. Proc Natl Acad Sci 100:14806–14811

Fukunaka Y, Shinkai T, Hwang R, Hori H, Utsunomiya K, Sakata S, Naoe Y, Shimizu K, Matsumoto C, Ohmori O, Nakamura J (2007) The orexin 1 receptor (HCRTR1) gene as a susceptibility gene contributing to polydipsia-hyponatremia in schizophrenia. Neuromolecular Med 9:292–297

Fulcher BD, Phillips AJ, Postnova S, Robinson PA (2014) A physiologically based model of orexinergic stabilization of sleep and wake. PLoS ONE 9:e91982

Germain A, Kupfer DJ (2008) Circadian rhythm disturbances in depression. Human Psychopharmacol Clin Exp 23:571–585

Goldbeter A (1995) A model for circadian oscillations in the Drosophila period protein (PER). Proc Roy Soc Lond Ser B Biol Sci 261:319–324

Goncalves L, Sego C, Metzger M (2012) Differential projections from the lateral habenula to the rostromedial tegmental nucleus and ventral tegmental area in the rat. J Comp Neurol 520:1278–1300

Gonzalez R (2014) The relationship between bipolar disorder and biological rhythms. J Clin Psychiatry 75:e323–e331

Gonze D, Bernard S, Waltermann C, Kramer A, Herzel H (2005) Spontaneous synchronization of coupled circadian oscillators. Biophys J 89:120–129

Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, Reid I, Hall J, Steele JD (2011) Expected value and prediction error abnormalities in depression and schizophrenia. Brain 134:1751–1764

Grzanna R, Molliver M (1980) The locus coeruleus in the rat: an immunohistochemical delineation. Neuroscience 5:21–40

Guilding C, Piggins HD (2007) Challenging the omnipotence of the suprachiasmatic timekeeper: are circadian oscillators present throughout the mammalian brain? Eur J Neurosci 25:3195–3216

Hasler G (2010) Pathophysiology of depression: do we have any solid evidence of interest to clinicians? World Psychiatry 9:155–161

Hassani OK, Lee MG, Henny P, Jones BE (2009) Discharge profiles of identified GABAergic in comparison to cholinergic and putative glutamatergic basal forebrain neurons across the sleep–wake cycle. J Neurosci 29:11828–11840

Hassani OK, Henny P, Lee MG, Jones BE (2010) GABAergic neurons intermingled with orexin and MCH neurons in the lateral hypothalamus discharge maximally during sleep. Eur J Neurosci 32:448–457

Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, Berson DM (2006) Central projections of melanopsin-expressing retinal ganglion cells in the mouse. Journal of Comparative Neurology 497:326–349

Herkenham M, Nauta WJ (1979) Efferent connections of the habenular nuclei in the rat. J Comp Neurol 187:19-47

Herkenham M, Nauta WJ (1993) Afferent connections of the habenular nuclei in the rat. A horseradish peroxidase study, with a note on the fiber-of-passage problem. Neuroanatomy Springer 277–299

Huang ZL, Zhang Z, Qu WM (2014) Roles of adenosine and its receptors in sleep-wake regulation. Int Rev Neurobiol 119:349–371

Hughes AT, Piggins HD (2012) Feedback actions of locomotor activity to the circadian clock. Prog Brain Res 199:305–336

Huys QJ, Pizzagalli DA, Bogdan R, Dayan P (2013) Mapping anhedonia onto reinforcement learning: a behavioural meta-analysis. Biol Mood Anxiety Disord 3:12

Iitaka C, Miyazaki K, Akaike T, Ishida N (2005) A role for glycogen synthase kinase-3beta in the mammalian circadian clock. J Biol Chem 280:29397–29402

Ito N, Yabe T, Gamo Y, Nagai T, Oikawa T, Yamada H, Hanawa T (2008) Icv administration of orexin-A induces an antidepressive-like effect through hippocampal cell proliferation. Neuroscience 157:720–732

Jalewa J, Joshi A, McGinnity TM, Prasad G, Wong-Lin K, Holscher C (2014a) Neural circuit interactions between the dorsal raphe nucleus and the lateral hypothalamus: an experimental and computational study. PLoS ONE 9:e88003

Jalewa J, Wong-Lin K, McGinnity TM, Prasad G, Hölscher C (2014b) Increased number of orexin/hypocretin neurons with high and prolonged external stress-induced depression. Behav Brain Res 272:196–204

Jankowski MP, Sesack SR (2004) Prefrontal cortical projections to the rat dorsal raphe nucleus: ultrastructural features and associations with serotonin and gamma-aminobutyric acid neurons. J Comp Neurol 468:518–529

Jones BE, Moore RY (1977) Ascending projections of the locus coeruleus in the rat II. Autoradiographic study. Brain Res 127:25–53

Joshi A, Wong-Lin K, Mcginnity TM, Prasad G (2011) A mathematical model to explore the interdependence between the serotonin and orexin/hypocretin systems. In: Proceedings of conference on IEEE engineering in medicine and biology society, pp 7270–7273

Kalen P, Skagerberg G, Lindvall O (1988) Projections from the ventral tegmental area and mesencephalic raphe to the dorsal raphe nucleus in the rat. Exp Brain Res 73:69–77

Kantor S, Mochizuki T, Janisiewicz AM, Clark E, Nishino S, Scammell TE (2009) Orexin neurons are necessary for the circadian control of REM sleep. Sleep 32:1127–1134

Kawato M, Fujita K, Suzuki R, Winfree AT (1982) A three-oscillator model of the human circadian system controlling the core temperature rhythm and the sleep-wake cycle. J Theor Biol 98:369–392

Keers R, Pedroso I, Breen G, Aitchison KJ, Nolan PM, Cichon S, Nothen MM, Rietschel M, Schalkwyk LC, Fernandes C (2012) Reduced anxiety and depression-like behaviours in the circadian period mutant mouse afterhours. PLoS ONE 7:e38263

Kim MA, Lee HS, Lee BY, Waterhouse BD (2004) Reciprocal connections between subdivisions of the dorsal raphe and the nuclear core of the locus coeruleus in the rat. Brain research 1026:56–67

Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, Ordway GA (1997) Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 17:8451–8458

Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455:894–902

Kronauer RE, Czeisler CA, Pilato SF, Moore-Ede MC, Weitzman ED (1982) Mathematical model of the human circadian system with two interacting oscillators. Am J Physiol-Regul Integr Comp Physiol 242:R3–R17

Kronauer R, Czeisler C, Pilato S, Moore-Ede M, Weitzman E (1983) Mathematical representation of the human circadian system: two interacting oscillators which affect sleep. Sleep Dis Basic Clin Res 173–194

Kumar R, Bose A, Mallick BN (2012) A mathematical model towards understanding the mechanism of neuronal regulation of wake-NREMS-REMS states. PLoS ONE 7:e42059

Kuru M, Ueta Y, Serino R, Nakazato M, Yamamoto Y, Shibuya I, Yamashita H (2000) Centrally administered orexin/hypocretin activates HPA axis in rats. NeuroReport 11:1977–1980

Laasonen-Balk T, Kuikka J, Viinamaki H, Husso-Saastamoinen M, Lehtonen J, Tiihonen J (1999) Striatal dopamine transporter density in major depression. Psychopharmacology 144:282–285

Lambe EK, Liu RJ, Aghajanian GK (2007) Schizophrenia, hypocretin (orexin), and the thalamocortical activating system. Schizophr Bull 33:1284–1290

Landgraf D, McCarthy MJ, Welsh DK (2014) The role of the circadian clock in animal models of mood disorders. Behav Neurosci 128:344–359

Lanni C, Govoni S, Lucchelli A, Boselli C (2009) Depression and antidepressants: molecular and cellular aspects. Cell Mol Life Sci 66:2985–3008

Laposky A, Easton A, Dugovic C, Walisser J, Bradfield C, Turek F (2005) Deletion of the mammalian circadian clock gene BMAL1/Mop3 alters baseline sleep architecture and the response to sleep deprivation. Sleep 28:395–409

Laviale A, Weiss T, Veh RW, Mcginnity T, Maguire L, Wong-Lin K (2013) A single spiking neuronal model to account for the diverse spontaneous firing patterns of lateral habenula neurons. Society for Neuroscience, Washington DC

Lee HS, Lee BY, Waterhouse BD (2005a) Retrograde study of projections from the tuberomammillary nucleus to the dorsal raphe and the locus coeruleus in the rat. Brain Res 1043:65–75

Lee MG, Hassani OK, Jones BE (2005b) Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. J Neurosci 25:6716–6720

Leibowitz SF, Shor-Posner G (1986) Brain serotonin and eating behavior. Appetite 7:1–14

Leloup J-C, Goldbeter A (2003) Toward a detailed computational model for the mammalian circadian clock. Proc Natl Acad Sci 100:7051–7056

Li J, Lu WQ, Beesley S, Loudon AS, Meng QJ (2012) Lithium impacts on the amplitude and period of the molecular circadian clockwork. PLoS ONE 7:e33292

Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, Qiu X, de Jong PJ, Nishino S, Mignot E (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell 98:365–376

López M, Tena-Sempere M, Diéguez C (2010) Cross-talk between orexins (hypocretins) and the neuroendocrine axes (hypothalamic–pituitary axes). Front Neuroendocrinol 31:113–127

Madaan V, Wilson DR (2009) Neuropeptides: relevance in treatment of depression and anxiety disorders. Drug News Perspect 22:319–324

Mahler SV, Moorman DE, Smith RJ, James MH, Aston-Jones G (2014) Motivational activation: a unifying hypothesis of orexin/hypocretin function. Nat Neurosci 17:1298–1303

Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L, Sanacora G, Owens MJ, Nemeroff CB, Rajeevan N (1998) Reduced brain serotonin transporter availability in major depression as measured by [123 I]-2β-carbomethoxy-3β-(4-iodophenyl) tropane and single photon emission computed tomography. Biol Psychiatry 44:1090–1098

Mang GM, Durst T, Burki H, Imobersteg S, Abramowski D, Schuepbach E, Hoyer D, Fendt M, Gee CE (2012) The dual orexin receptor antagonist almorexant induces sleep and decreases orexin-induced locomotion by blocking orexin 2 receptors. Sleep 35:1625–1635

Manns ID, Alonso A, Jones BE (2000) Discharge profiles of juxtacellularly labeled and immunohistochemically identified GABAergic basal forebrain neurons recorded in association with the electroencephalogram in anesthetized rats. J Neurosci 20:9252–9263

Marston OJ, Williams RH, Canal MM, Samuels RE, Upton N, Piggins HD (2008) Circadian and dark-pulse activation of orexin/hypocretin neurons. Mol Brain 1:19

Mathers CD, Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. PLoS medicine 3:e442

Mazzocchi G, Malendowicz LK, Gottardo L, Aragona F, Nussdorfer GG (2001) Orexin A stimulates cortisol secretion from human adrenocortical cells through activation of the adenylate cyclase-dependent signaling cascade. J Clin Endocrinol Metab 86:778–782

McCarthy MJ, Welsh DK (2012) Cellular circadian clocks in mood disorders. J Biol Rhythms 27:339–352

McClung CA, Sidiropoulou K, Vitaterna M, Takahashi JS, White FJ, Cooper DC, Nestler EJ (2005) Regulation of dopaminergic transmission and cocaine reward by the Clock gene. Proc Natl Acad Sci U S A 102:9377–9381

McGranaghan PA, Piggins HD (2001) Orexin A-like immunoreactivity in the hypothalamus and thalamus of the Syrian hamster (*Mesocricetus auratus*) and Siberian hamster (*Phodopus sungorus*), with special reference to circadian structures. Brain Res 904:234–244

Menet JS, Rosbash M (2011) When brain clocks lose track of time: cause or consequence of neuropsychiatric disorders. Curr Opin Neurobiol 21:849–857

Meyer JH, Kruger S, Wilson AA, Christensen BK, Goulding VS, Schaffer A, Minifie C, Houle S, Hussey D, Kennedy SH (2001) Lower dopamine transporter binding potential in striatum during depression. NeuroReport 12:4121–4125

Mieda M, Hasegawa E, Kisanuki YY, Sinton CM, Yanagisawa M, Sakurai T (2011) Differential roles of orexin receptor-1 and -2 in the regulation of non-REM and REM sleep. J Neurosci 31:6518–6526

Mikrouli E, Wörtwein G, Soylu R, Mathé AA, Petersén Å (2011) Increased numbers of orexin/hypocretin neurons in a genetic rat depression model. Neuropeptides 45:401–406

Mileykovskiy BY, Kiyashchenko LI, Siegel JM (2005) Behavioral correlates of activity in identified hypocretin/orexin neurons. Neuron 46:787–798

Mintun MA, Sheline YI, Moerlein SM, Vlassenko AG, Huang Y, Snyder AZ (2004) Decreased hippocampal 5-HT 2A receptor binding in major depressive disorder: in vivo measurement with [18 F] altanserin positron emission tomography. Biol Psychiatry 55:217–224

Mohawk JA, Takahashi JS (2011) Cell autonomy and synchrony of suprachiasmatic nucleus circadian oscillators. Trends Neurosci 34:349–358

Moret C, Briley M (2011) The importance of norepinephrine in depression. Neuropsychiatric Dis Treat 7:9

Mosqueiro T, De Lecea L, Huerta R (2014) Control of sleep-to-wake transitions via fast aminoacid and slow neuropeptide transmission. New J Phys 16

Mukherjee S, Coque L, Cao JL, Kumar J, Chakravarty S, Asaithamby A, Graham A, Gordon E, Enwright JF, 3RD, Dileone RJ, Birnbaum SG, Cooper DC, Mcclung CA (2010) Knockdown of Clock in the ventral tegmental area through RNA interference results in a mixed state of mania and depression-like behavior. Biol Psychiatry 68:503–511

Murray G, Harvey A (2010) Circadian rhythms and sleep in bipolar disorder. Bipolar Disord 12:459–472

Muschamp JW, Hollander JA, Thompson JL, Voren G, Hassinger LC, Onvani S, Kamenecka TM, Borgland SL, Kenny PJ, Carlezon WA Jr (2014) Hypocretin (orexin) facilitates reward by attenuating the antireward effects of its cotransmitter dynorphin in ventral tegmental area. Proc Natl Acad Sci U S A 111:E1648–E1655

Nakamura K, Wong-Lin K (2014) Functions and computational principles of serotonergic and related systems at multiple scales. Front Integr Neurosci 8:23

Nambu T, Sakurai T, Mizukami K, Hosoya Y, Yanagisawa M, Goto K (1999) Distribution of orexin neurons in the adult rat brain. Brain Res 827:243–260

Naylor E, Bergmann BM, Krauski K, Zee PC, Takahashi JS, Vitaterna MH, Turek FW (2000) The circadian clock mutation alters sleep homeostasis in the mouse. J Neurosci 20:8138–8143

Nemeroff CB (1998) The neurobiology of depression. Sci Am-Am Edit 278:42–49

Nollet M, Leman S (2013) Role of orexin in the pathophysiology of depression: potential for pharmacological intervention. CNS Drugs 27:411–422

Nollet M, Gaillard P, Tanti A, Girault V, Belzung C, Leman S (2012) Neurogenesis-independent antidepressant-like effects on behavior and stress axis response of a dual orexin receptor antagonist in a rodent model of depression. Neuropsychopharmacology 37:2210–2221

Ogawa SK, Cohen JY, Hwang D, Uchida N, Watabe-Uchida M (2014) Organization of monosynaptic inputs to the serotonin and dopamine neuromodulatory systems. Cell reports 8:1105–1118

Omelchenko N, Bell R, Sesack SR (2009) Lateral habenula projections to dopamine and GABA neurons in the rat ventral tegmental area. Eur J Neurosci 30:1239–1250

Onge JRS, Stopper CM, Zahm DS, Floresco SB (2012) Separate prefrontal-subcortical circuits mediate different components of risk-based decision making. J Neurosci 32:2886–2899

Ordway GA, Schenk J, Stockmeier CA, May W, Klimek V (2003) Elevated agonist binding to α 2-adrenoceptors in the locus coeruleus in major depression. Biol Psychiatry 53:315–323

Overstreet DH (1986) Selective breeding for increased cholinergic function: development of a new animal model of depression. Biol Psychiatry 21:49–58

Overstreet DH, Friedman E, Mathé AA, Yadid G (2005) The Flinders Sensitive Line rat: a selectively bred putative animal model of depression. Neurosci Biobehav Rev 29:739–759

Owens MJ, Nemeroff CB (1994) Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin Chem 40:288–295

Pandi-Perumal SR, Moscovitch A, Srinivasan V, Spence DW, Cardinali DP, Brown GM (2009) Bidirectional communication between sleep and circadian rhythms and its implications for depression: lessons from agomelatine. Prog Neurobiol 88:264–271

Park S, Harrold JA, Widdowson PS, Williams G (1999) Increased binding at 5-HT 1A, 5-HT 1B, and 5-HT 2A receptors and 5-HT transporters in diet-induced obese rats. Brain research 847:90–97

Patriarca M, Postnova S, Braun HA, Hernandez-Garcia E, Toral R (2012) Diversity and noise effects in a model of homeostatic regulation of the sleep-wake cycle. PLoS Comput Biol 8: e1002650

Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, Kilduff TS (1998) Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 18:9996–10015

Peyron C, Faraco J, Rogers W, Ripley B, Overeem S, Charnay Y, Nevsimalova S, Aldrich M, Reynolds D, Albin R, Li R, Hungs M, Pedrazzoli M, Padigaru M, Kucherlapati M, Fan J, Maki R, Lammers GJ, Bouras C, Kucherlapati R, Nishino S, Mignot E (2000) A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med 6:991–997

Phillips AJ, Robinson PA (2007) A quantitative model of sleep-wake dynamics based on the physiology of the brainstem ascending arousal system. J Biol Rhythms 22:167–179

Pietraszek MH, Takahashi S, Takada Y, Ohara K, Inatomi H, Kondo N, Ohara K, Takada A (1991) Diurnal patterns of serotonin, 5-hydroxyindoleacetic acid, tryptophan and fibrinolytic activity in blood of depressive patients and healthy volunteers. Thromb Res 64:243–252

Piggins HD, Guilding C (2011) The neural circadian system of mammals. Essays Biochem 49:1–17

Poirier S, Legris G, Tremblay P, Michea R, Viau-Guay L, Merette C, Bouchard RH, Maziade M, Roy MA (2010) Schizophrenia patients with polydipsia and water intoxication are characterized by greater severity of psychotic illness and a more frequent history of alcohol abuse. Schizophr Res 118:285–291

Postnova S, Voigt K, Braun HA (2009) A mathematical model of homeostatic regulation of sleep-wake cycles by hypocretin/orexin. J Biol Rhythms 24:523–535

Proulx CD, Hikosaka O, Malinow R (2014) Reward processing by the lateral habenula in normal and depressive behaviors. Nat Neurosci 17:1146–1152

Pujara M, Koenigs M (2014) Mechanisms of reward circuit dysfunction in psychiatric illness: prefrontal-striatal interactions. Neuroscientist 20:82–95

Qu Z, Garfinkel A, Weiss JN, Nivala M (2011) Multi-scale modeling in biology: how to bridge the gaps between scales? Prog Biophys Mol Biol 107:21–31

Quintana J (1992) Platelet serotonin and plasma tryptophan decreases in endogenous depression. Clinical, therapeutic, and biological correlations. J Affect Disord 24:55–62

Rajkowska G (2000) Histopathology of the prefrontal cortex in major depression: what does it tell us about dysfunctional monoaminergic circuits? Prog Brain Res 126:397–412

Rempe MJ, Best J, Terman D (2010) A mathematical model of the sleep/wake cycle. J Math Biol 60:615–644

Root DH, Mejias-Aponte CA, Qi J, Morales M (2014) Role of glutamatergic projections from ventral tegmental area to lateral habenula in aversive conditioning. J Neurosci 34:13906–13910

Roybal K, Theobold D, Graham A, Dinieri JA, Russo SJ, Krishnan V, Chakravarty S, Peevey J, Oehrlein N, Birnbaum S, Vitaterna MH, Orsulak P, Takahashi JS, Nestler EJ, Carlezon WA Jr, Mcclung CA (2007) Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci U S A 104:6406–11

Ruhe HG, Mason NS, Schene AH (2007) Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry 12:331–359

Saar I, Lahe J, Langel K, Runesson J, Webling K, Jarv J, Rytkonen J, Narvanen A, Bartfai T, Kurrikoff K, Langel U (2013) Novel systemically active galanin receptor 2 ligands in depression-like behavior. J Neurochem 127:114–123

Sakhi K, Belle MD, Gossan N, Delagrange P, Piggins HD, (2014) Daily variation in the electrophysiological activity of mouse medial habenula neurones. J physiol 592:587–603

Sakurai T (2006) Roles of orexins and orexin receptors in central regulation of feeding behavior and energy homeostasis. CNS Neurol Disorders-Drug Targets (Formerly Curr Drug Targets-CNS Neurol Disorders) 5:313–325

Sakurai T (2007) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci 8:171–181

Sakurai T (2014) The role of orexin in motivated behaviours. Nat Rev Neurosci 15:719–731

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 92:573–585

Sakurai T, Mieda M, Tsujino N (2010) The orexin system: roles in sleep/wake regulation. Ann N Y Acad Sci 1200:149–161

Salomon RM, Ripley B, Kennedy JS, Johnson B, Schmidt D, Zeitzer JM, Nishino S, Mignot E (2003) Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects. Biol Psychiatry 54:96–104

Saper CB, Chou TC, Scammell TE (2001) The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 24:726–731

Sarchiapone M, Carli V, Camardese G, Cuomo C, di Giuda D, Calcagni M-L, Focacci C, de Risio S (2006) Dopamine transporter binding in depressed patients with anhedonia. Psychiatry Res Neuroimaging 147:243–248

Schmidt FM, Brugel M, Kratzsch J, Strauss M, Sander C, Baum P, Thiery J, Hegerl U, Schonknecht P (2010) Cerebrospinal fluid hypocretin-1 (orexin A) levels in mania compared to unipolar depression and healthy controls. Neurosci Lett 483:20–22

Schnell A, Albrecht U, Sandrelli F (2014) Rhythm and mood: relationships between the circadian clock and mood-related behavior. Behav Neurosci 128:326–343

Schone C, Apergis-Schoute J, Sakurai T, Adamantidis A, Burdakov D (2014) Coreleased orexin and glutamate evoke nonredundant spike outputs and computations in histamine neurons. Cell Rep 7:697–704

Schwartz MD, Urbanski HF, Nunez AA, Smale L (2011) Projections of the suprachiasmatic nucleus and ventral subparaventricular zone in the Nile grass rat (*Arvicanthis niloticus*). Brain Res 1367:146–161

Segal M (1979) Serotonergic innervation of the locus coeruleus from the dorsal raphe and its action on responses to noxious stimuli. J Physiol 286:401–415

Sidor MM, Spencer SM, Dzirasa K, Parekh PK, Tye KM, Warden MR, Arey RN, Enwright JF, 3RD, Jacobsen JP, Kumar S, Remillard EM, Caron MG, Deisseroth K, Mcclung CA (2015) Daytime spikes in dopaminergic activity drive rapid mood-cycling in mice. Mol Psychiatry 5

Siegle GJ (1999) A neural network model of attention biases in depression. Prog Brain Res 121:407–432

Siegle GJ, Hasselmo ME (2002) Using connectionist models to guide assessment of psychological disorder. Psychol Assess 14:263–278

Sim CK, Forger DB (2007) Modeling the electrophysiology of suprachiasmatic nucleus neurons. J Biol Rhythms 22:445–453

Sims RE, Wu HH, Dale N (2013) Sleep-wake sensitive mechanisms of adenosine release in the basal forebrain of rodents: an in vitro study. PLoS ONE 8:e53814

Smith CM, Walker AW, Hosken IT, Chua BE, Zhang C, Haidar M, Gundlach AL (2014) Relaxin-3/RXFP3 networks: an emerging target for the treatment of depression and other neuropsychiatric diseases? Frontiers Pharmacol 5

Sorooshyari S, Huerta R, De_Lecea L (2015) A framework for quantitative modeling of neural circuits involved in sleep-to-wake transition. Name Frontiers Neurol 6:32

Spinazzi R, Andreis PG, Rossi GP, Nussdorfer GG (2006) Orexins in the regulation of the hypothalamic-pituitary-adrenal axis. Pharmacol Rev 58:46–57

Stamatakis AM, Jennings JH, Ung RL, Blair GA, Weinberg RJ, Neve RL, Boyce F, Mattis J, Ramakrishnan C, Deisseroth K (2013) A unique population of ventral tegmental area neurons inhibits the lateral habenula to promote reward. Neuron 80:1039–1053

Strogatz SH (1987) Open peer. Commentary the mathematical structure of the human sleep-wake cycle. In: Strogatz SH (1986) Lecture notes in biomathematics, vol 69. Springer, Berlin. J Biol Rhythms 2:317–329

Strogatz S, Carpenter G (1986) A comparative analysis of models of the human sleep-wake cycle. Lect Math Life Sci 19:1–38

Thase ME, Trivedi MH, Rush AJ (1995) MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 12:185–219

Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, Ptacek LJ, Fu YH (2001) An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science 291:1040–1043

Torterolo P, Chase MH (2014) The hypocretins (orexins) mediate the "phasic" components of REM sleep: a new hypothesis. Sleep Sci 7:19–29

Tsujino N, Sakurai T (2009) Orexin/hypocretin: a neuropeptide at the interface of sleep, energy homeostasis, and reward system. Pharmacol Rev 61:162–176

Tsuno N, Besset A, Ritchie K (2005) Sleep and depression. J Clin Psychiatry 66:1254–1269

Valdizán EM, Díez-Alarcia R, González-Maeso J, Pilar-Cuéllar F, García-Sevilla JA, Meana JJ, Pazos A (2010) α 2-Adrenoceptor functionality in postmortem frontal cortex of depressed suicide victims. Biol Psychiatry 68:869–872

van Oosterhout F, Lucassen EA, Houben T, Vanderleest HT, Antle MC, Meijer JH (2012) Amplitude of the SCN clock enhanced by the behavioral activity rhythm. PLoS ONE 7:e39693

Vasalou C, Henson MA (2010) A multiscale model to investigate circadian rhythmicity of pacemaker neurons in the suprachiasmatic nucleus. PLoS Comput Biol 6:e1000706

Vertes RP, Linley SB (2008) Efferent and afferent connections of the dorsal and median raphe nuclei in the rat. Serotonin and sleep: molecular, functional and clinical aspects Springer 4:69

Vitaterna MH, King DP, Chang AM, Kornhauser JM, Lowrey PL, McDonald JD, Dove WF, Pinto LH, Turek FW, Takahashi JS (1994) Mutagenesis and mapping of a mouse gene, clock, essential for circadian behavior. Science 264:719–725

Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW (2009) Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry 66:617–626

Walderhaug E, Varga M, San Pedro M, Hu J, Neumeister A (2011) The role of the aminergic systems in the pathophysiology of bipolar disorder. In: Behavioral neurobiology of bipolar disorder and its treatment. Springer, Berlin

Wang DH, Wong-Lin K (2013) Comodulation of dopamine and serotonin on prefrontal cortical rhythms: a theoretical study. Front Integr Neurosci 7:54

Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N (2012) Whole-brain mapping of direct inputs to midbrain dopamine neurons. Neuron 74:858–873

Webb IC, Patton DF, Hamson DK, Mistlberger RE (2008) Neural correlates of arousal-induced circadian clock resetting: hypocretin/orexin and the intergeniculate leaflet. Eur J Neurosci 27:828–835

Wehr TA, Sack D, Rosenthal N, Duncan W, Gillin JC (1983) Circadian rhythm disturbances in manic-depressive illness. Fed Proc 42:2809–2814

Welsh DK, Moore-Ede MC (1990) Lithium lengthens circadian period in a diurnal primate, *Saimiri sciureus*. Biol Psychiatry 28:117–126

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N (2013) Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382:1575–1586

Williams KS, Behn CG (2011) Dynamic interactions between orexin and dynorphin may delay onset of functional orexin effects: a modeling study. J Biol Rhythms 26:171–181

Wilson HR, Cowan JD (1972) Excitatory and inhibitory interactions in localized populations of model neurons. Biophys J 12:1–24

Winfree AT (1983) Impact of a circadian clock on the timing of human sleep. Am J Physiol-Regul Integr Comp Physiol 245:R497–R504

Wirz-Justice A (2008) Diurnal variation of depressive symptoms. Dialogues Clin Neurosci 10:337–343

Wong-Lin K, Joshi A, Prasad G, McGinnity TM (2012) Network properties of a computational model of the dorsal raphe nucleus. Neural Netw 32:15–25

Wulff K, Gatti S, Wettstein JG, Foster RG (2010) Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci 11:589–599

Wulff K, Dijk D-J, Middleton B, Foster RG, Joyce EM (2012) Sleep and circadian rhythm disruption in schizophrenia. Br J Psychiatry 200:308–316

Yamada Y, Forger D (2010) Multiscale complexity in the mammalian circadian clock. Curr Opin Genet Dev 20:626–633

Yeoh JW, Campbell EJ, James MH, Graham BA, Dayas CV (2014) Orexin antagonists for neuropsychiatric disease: progress and potential pitfalls. Front Neurosci 8:36

Yoshida Y, Fujiki N, Nakajima T, Ripley B, Matsumura H, Yoneda H, Mignot E, Nishino S (2001) Fluctuation of extracellular hypocretin-1 (orexin A) levels in the rat in relation to the light–dark cycle and sleep–wake activities. J Neurosci 14:1075–1081

Yu X, Zecharia A, Zhang Z, Yang Q, Yustos R, Jager P, Vyssotski AL, Maywood ES, Chesham JE, Ma Y, Brickley SG, Hastings MH, Franks NP, Wisden W (2014) Circadian factor BMAL1 in histaminergic neurons regulates sleep architecture. Curr Biol 24:2838–2844

Zhang S, Zeitzer JM, Yoshida Y, Wisor JP, Nishino S, Edgar DM, Mignot E (2004) Lesions of the suprachiasmatic nucleus eliminate the daily rhythm of hypocretin-1 release. Sleep 27:619–627

Ziolkowska A, Spinazzi R, Albertin G, Nowak M, Malendowicz LK, Tortorella C, Nussdorfer GG (2005) Orexins stimulate glucocorticoid secretion from cultured rat and human adrenocortical cells, exclusively acting via the OX1 receptor. J Steroid Biochem Mol Biol 96:423–429