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Sleep and circadian rhythm disruption in neuropsychiatric illness

Aarti Jagannath[1,2], Stuart N Peirson[1] and Russell G Foster[1]

Sleep and circadian rhythm disruption (SCRD) is a common feature in many neuropsychiatric diseases including schizophrenia, bipolar disorder and depression. Although the precise mechanisms remain unclear, recent evidence suggests that this comorbidity is not simply a product of medication or an absence of social routine, but instead reflects commonly affected underlying pathways and mechanisms. For example, several genes intimately involved in the generation and regulation of circadian rhythms and sleep have been linked to psychiatric illness. Further, several genes linked to mental illness have recently been shown to also play a role in normal sleep and circadian behaviour. Here we describe some of the emerging common mechanisms that link circadian rhythms, sleep and SCRD in severe mental illnesses. A deeper understanding of these links will provide not only a greater understanding of disease mechanisms, but also holds the promise of novel avenues for therapeutic intervention.

Addresses
[1] Department of Clinical Neurosciences (Nuffield Laboratory of Ophthalmology), University of Oxford, Level 5-6 West Wing, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, United Kingdom
[2] F.Hoffmann-La Roche AG, Pharma Research & Early Development, DTA Neuroscience pRED Grenzacherstrasse 124, Basel CH4070, Switzerland

Corresponding authors: Peirson, Stuart N (stuart.peirson@eye.ox.ac.uk) and Foster, Russell G (russell.foster@eye.ox.ac.uk)

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Introduction

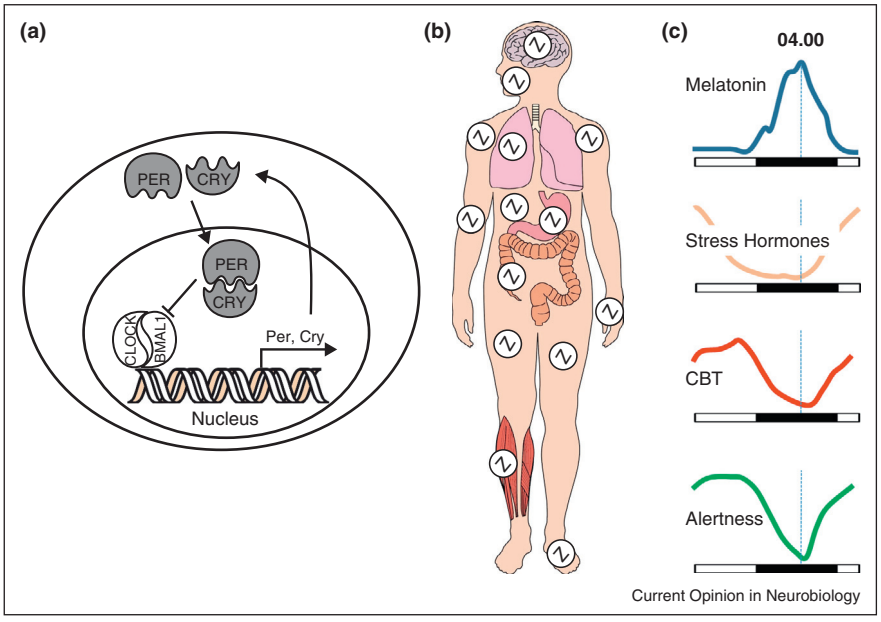
Sleep disruption is a notable and long-recognized feature of mental illness. The majority of patients with schizophrenia, bipolar disorder and major depressive disorder report sleep disturbances, although the mechanistic relationship between these neuropsychiatric illnesses and sleep remains unclear [1•]. Sleep/wake cycles are partially regulated by the circadian clock and recent studies have implicated circadian disruption, both at the level of clock genes themselves and clock outputs, in the aetiology of these disorders. Here we consider the major developments in the last few years linking the circadian clock and sleep with neuropsychiatric disease.

Circadian rhythms and sleep: from basic mechanisms to health

The Earth's 24 hour cycle of light and darkness results in a predictably changing environment, providing a key selective advantage to organisms that are able to anticipate and exploit these rhythmic changes. Consequently, most aspects of physiology and behaviour display 24 hour variations, driven by an endogenous circadian clock (from the Latin *circa* — approximately and *diem* — day). In mammals, the mechanism providing this rhythm is a molecular transcriptional-translational feedback loop (TTFL), consisting of the transcription factors CLOCK and BMAL1 which drive the expression of clock genes including *Period* and *Cryptochrome* that in turn feed-back to regulate their own expression (Figure 1a) [2]. This TTFL also regulates the expression of clock-controlled genes in a rhythmic manner, resulting in the oscillation of tissue-specific metabolic and physiological functions. This molecular oscillator mechanism is found in most cells throughout the body. As a result, the circadian system comprises a network of synchronized cell autonomous 24 hour oscillators that fine-tune physiology and behaviour to the varied demands of the environmental day [3]. This synchronization is achieved via a master circadian pacemaker, which in mammals, is located in the suprachiasmatic nuclei (SCN) in the ventral hypothalamus [4]. The SCN clock is in-turn entrained by the environmental light/dark cycle, detected by retinal photoreceptors (rods, cones and melanopsin-containing photosensitive ganglion cells) and relayed via the retinohypothalamic tract [5]. Ill-defined neural and hormonal signals from the SCN, and feedbacks from peripheral outputs, result in an entrained and synchronized temporal network (Figure 1b,c). If the signals necessary for entrainment of central and peripheral oscillators are uncoupled, clocks in different tissues can become desynchronized, resulting in a state of internal desynchrony as experienced in jet lag [6].

The sleep/wake cycle is perhaps the most familiar circadian cycle. However, in addition to the circadian clock, sleep is also regulated by homeostatic processes. Sleep homeostasis can be defined as the sleep/wake-dependent aspect of sleep regulation, such that an increase in sleep propensity occurs when sleep is absent/curtailed, whilst sleep propensity is reduced in response to excess sleep [7]. The precise mechanisms involved remain unclear. However, adenosine has emerged as a clear candidate, levels of which rise in the basal forebrain during wakefulness and fall during sleep [8•]. In addition, light levels, social cues, stress hormones and melatonin all play key modulatory roles in sleep. Sleep itself arises from the

Figure 1



Generation of circadian rhythms and their role in the regulation of physiology. **(a)** The molecular clock comprises a transcriptional-translational feedback loop of the transcription factors CLOCK and BMAL1 which drive the expression of *Per* and *Cry*, in addition to a host of genes regulating physiology and metabolism. PER and CRY in turn repress CLOCK:BMAL, thereby autoregulating their own expression. The period of this loop is around 24 hours. **(b)** In humans, the master clock is housed in the SCN, and this clock communicates and entrains the peripheral clocks of the body, resulting in coordinated rhythmic physiological outputs. **(c)** Examples of such outputs include (from upper to lower) the regulation of melatonin secretion by the pineal, the level of stress hormones, the regulation of core body temperature (CBT) and alertness levels.

interaction between multiple brain nuclei and neurotransmitter systems that collectively either promote sleep or wakefulness, (see [9,10] for details). The resulting coordinated neuronal activity gives rise to changes in activity patterns, body posture and responsiveness to stimuli, all of which characterize the sleep/wake states [11].

In addition to the sleep/wake cycle, many of our metabolic and physiological functions, including the regulation of body temperature and blood pressure display marked circadian rhythms [12]. Both are closely linked with sleep, and for a long time, were thought to be a part of the sleep response. However, lesion studies on rats demonstrated that body temperature and sleep are regulated separately by the circadian system [13]. Given the pivotal role of the circadian clock, one would predict that disruptions either of the clock itself or of the downstream components of the circadian timing system can cause pathological changes in metabolism and physiology. The reasons for this are two-fold: firstly, changes in circadian timing cause desynchrony amongst the multiple oscillators within the circadian network and the environment; secondly, CLOCK and BMAL1 are transcription factors that directly control the expression of many genes that regulate metabolism and other aspects of physiology. Indeed, mice with mutations in the circadian clock genes *Clock* and *Bmal1* are obese, hyperglyceamic and hypoinsulineamic [14,15]. *Rev-erbA* and *Rev-erbB* are clock genes that function in concert with *Clock*, and double knock-out mice show severe disruption of lipid metabolism [16]. Further, several studies have shown interesting links between the circadian clock and drug/alcohol abuse (see [17] for details).

Circadian disruption can also profoundly impact sleep. Sleep disruption is associated with a wide range of emotional, cognitive and somatic disorders. There are strong links between sleep disruption and cognitive function, specifically in memory consolidation where learning improves significantly after a night of sleep, and this performance gain can be lost with disruption of just REM sleep [18,19]. Disrupted sleep impairs immune system function [20], with the activity of natural killer cells in humans reducing by as much as 28% after one night of sleep deprivation [21]. For a detailed review of the health consequences of sleep disruption see [11].

Sleep and circadian rhythm disruption (SCRD)

SCRD is a common feature of neuropsychiatric disease. This observation is not new. Indeed, in 1883 Emil Kraepelin described the association between abnormal sleep patterns and mental health [22], and the clear links between sleep and bipolar disorder were described over