# Circadian Disruption in Psychiatric Disorders

Stephanie G. Jones, PhD*, Ruth M. Benca, MD, PhD

**KEYWORDS**

• Circadian • Psychiatric • Depression • Bipolar disorder • Genetics • Schizophrenia

**KEY POINTS**

- The circadian system is responsible for the temporal organization of physiologic function, and disruptions can have marked functional impacts.
- Psychiatric illnesses are often associated with disruptions in circadian rhythms, including alterations in sleep timing, core body temperature rhythms, and melatonin and cortisol secretion.
- Presence of circadian disruption and efficacy of chronobiological interventions raise questions regarding how these abnormalities contribute to disease onset, progression, maintenance, and response to treatment.
- Questions remain whether as to whether circadian disruption leads to mental health problems, and/or whether the underlying pathophysiology of psychiatric illness leads to dysregulation of circadian physiology.

## INTRODUCTION

Nearly all psychiatric disorders present with circadian disruption, such as abnormalities in the timing of the sleep-wake cycle, core body temperature rhythms, and melatonin and cortisol secretion. The pathophysiologic significance of circadian abnormalities is a matter of debate, and is alternatively hypothesized to contribute to illness onset and progression (1) causally, as a direct result of genetic vulnerabilities in the circadian system that predispose to psychiatric illness; (2) secondarily, as a result of alterations in the timing of illness-related behavior leading to rhythm desynchronization; or (3) concomitantly, because of overlap in the molecular machinery and neural circuitry of psychiatric illness and the circadian system. In animal models of psychiatric disorders, there is evidence to suggest a causal link between circadian genes and behavioral disorders, but genetic data in humans are less compelling. Nevertheless, the presence of circadian disruption in the clinical profile of most psychiatric illnesses as well as the efficacy of chronobiological interventions raise questions about how circadian timing abnormalities may contribute to disease onset, progression, maintenance, and response to treatment. Most psychiatric disorders involve some measure of circadian disruption; however, this article focuses primarily on evidence for circadian pathology in the pathophysiology of mood disorders and schizophrenia. Although sleep disturbances are a cardinal feature of psychiatric disorders, specific sleep abnormalities are not reviewed in detail here; a large number of excellent reviews have recently been written on this topic.[1–5]

## CIRCADIAN SYSTEM: A BRIEF OVERVIEW

The circadian system is responsible for the temporal organization of virtually all aspect of physiology, including neuroendocrine function, body

Disclosure: The authors have nothing to disclose.
Department of Psychiatry, Center for Sleep Medicine and Sleep Research, University of Wisconsin-Madison, 6001 Research Park Boulevard, Madison, WI 53719, USA
* Corresponding author.
*E-mail address:* sgjones2@wisc.edu

Sleep Med Clin 10 (2015) 481–493
http://dx.doi.org/10.1016/j.jsmc.2015.07.004
1556-407X/15/$ – see front matter 

temperature, metabolic function, cognitive function, mood, and some aspects of the sleep-wake cycle. These rhythms are orchestrated by an endogenous master clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Fig. 1). Although the circadian system maintains the endogenous period ($\tau$) of rhythms in the absence of environmental input, without a force to entrain it to the environment, the length of this period is said to free run with a period close to, but not exactly, 24 hours. As such, the endogenous clock requires a regular resetting to ensure that the internal phase of the organism's clock is temporally aligned with that of the external world. This synchronization between the internal rhythm and the external world is achieved through exposure to a zeitgeber, or time giver. Although the light-dark cycle is the most potent zeitgeber for the SCN, other nonphotic factors, such as food availability, social interactions, and physical activity, can also entrain the clock or reset circadian phase of peripheral oscillators.[6] The importance of synchronization between the physiology of the organism and the external environment cannot be overstated; it ensures not only that the organism does the right thing at the right time of day but it also imposes temporal order between the myriad biochemical and physiologic systems within the body. The physical and mental malaise often seen in jet lag or shift work is a consequence of a misalignment between the SCN and the external day-night cycle as well as between central and peripheral rhythms.[7,8]

## *Molecular Mechanisms of Clock Function*

The circadian timing mechanism is fundamentally a cellular phenomenon, and the same core molecular machinery is responsible for creating and sustaining circadian rhythms in the SCN and

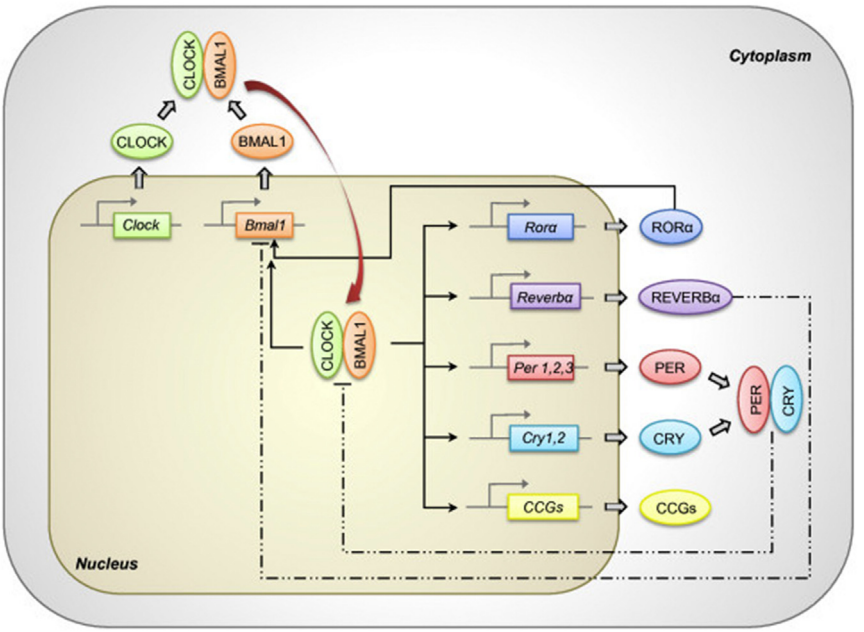


**Fig. 1.** Molecular machinery of the circadian clock. The core clock components CLOCK and BMAL1 heterodimerize in the cytoplasm, forming a protein complex. The heterodimer is then translocated to the nucleus and binds to E-boxes on the promoter of target genes, controlling their expression. These genes include Per1, Per2, Per3, Cry1, Cry2, Rev-erb$\alpha$, Ror$\alpha$, and many clock-controlled genes (CCGs). The CLOCK/BMAL1 heterodimer also stimulates transcription of Bmal1 itself, forming the positive feedback loop of the mechanism. The negative feedback loop is mainly regulated by CRY and PER, which heterodimerize in the cytoplasm, translocate to the nucleus, and inhibit CLOCK/BMAL1 transcription activity. Gene expression of Bmal1 is also regulated by REV-ERB$\alpha$ (inhibition) and ROR$\alpha$ (stimulation), which compete for the same ROR elements as are present in the Bmal1 promoter. Regulation of CCG expression by the circadian clock confers rhythmicity to a variety of molecular and physiologic processes. The *straight lines* indicate stimulation and the *dashed lines* indicate inhibition. (*From* Zanquetta MM, Corrêa-Giannella ML, Monteiro MB, et al. Body weight, metabolism, and clock genes. Diabetol Metab Syndr 2010;2:53. This article is open access, distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.)