Biological rhythms, higher brain function, and behavior: Gaps, opportunities, and challenges

Ruth Benca, Marilyn J. Duncan, Ellen Frank, Colleen McClung, Randy J. Nelson, Aleksandra Vicentic

ARTICLE INFO

Article history:
Accepted 15 September 2009
Available online 18 September 2009

ABSTRACT

Increasing evidence suggests that disrupted temporal organization impairs behavior, cognition, and affect; further, disruption of circadian clock genes impairs sleep–wake cycle and social rhythms which may be implicated in mental disorders. Despite this strong evidence, a gap in understanding the neural mechanisms of this interaction obscures whether biological rhythms disturbances are the underlying causes or merely symptoms of mental disorder. Here, we review current understanding, emerging concepts, gaps, and opportunities pertinent to (1) the neurobiology of the interactions between circadian oscillators and the neural circuits subserving higher brain function and behaviors of relevance to mental health, (2) the most promising approaches to determine how biological rhythms regulate brain function and behavior under normal and pathological conditions, (3) the gaps and challenges to advancing knowledge on the link between disrupted circadian rhythms/sleep and psychiatric disorders, and (4) the novel strategies for translation of basic science discoveries in circadian biology to clinical settings to define risk, prevent or delay onset of mental illnesses, design diagnostic tools, and propose new therapeutic strategies.

This review was developed from the National Institute of Mental Health workshop entitled “Neurobiological Basis of Circadian Rhythms Interaction with Complex Behavior” on July 22–23, 2008. The participants at the workshop were Gary Aston-Jones, Medical University of South Carolina; Ruth Benca, University of Wisconsin; Francesco Benedetti, Scientific Institute and University Vita-Salute San Raffaele; Mark Blumberg, University of Iowa; Mary Carskadon, Brown University School of Medicine, Christopher Colwell, UCLA; Marilyn Duncan, University of Kentucky Medical Center; Ellen Frank, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine; Colleen McClung, UT Southwestern Medical Center; Steven McKnight, UT Southwestern Medical Center; Randy J. Nelson, Ohio State University; Amita Sehgal, University of Pennsylvania; Jeffrey Sprouse, Lundbeck Research USA; Albert Stunkard, University of Pennsylvania; Joseph S. Takahashi, Northwestern University and UT Southwestern Medical Center; Giulio Tononi, University of Wisconsin; and Fred Turek, Northwestern University. The participants from the National Institute of Mental Health were Linda Brady; Guang Chen; Rebecca DelCarmen-Wiggins; Thomas Insel; Ellen Leibenluft; Richard Nakamura; Kevin Quinn; and Aleksandra Vicentic.

* Corresponding author.

E-mail address: vicentica@mail.nih.gov (A. Vicentic).

Abbreviations: CLOCK, circadian locomotor output cycles kaput; Npas2, neuronal PAS domain protein 2; Per1, period homologue 1 and 2; Cry1Cry2, cryptochrome 1and 2; GSK3-β, glycogen synthase kinase 3 beta; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; SPECT, single photon emission computed tomography; VIP, vasoactive intestinal peptide

0165-0173/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.brainresrev.2009.09.005
1. Introduction

Increasing evidence suggests that alterations in circadian rhythms can have profound consequences on emotional behavior and mental health. Circadian rhythms are endogenously driven biological variations that fluctuate with a periodicity of approximately 24 h and can be synchronized with the external temporal environment by light and non-photic cues. The master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) controls many physiological and behavioral variables via the orchestrated function of clock-controlled genes that regulate the output rhythms throughout the central nervous system and periphery. Disruptions in circadian clock genes that constitute the molecular basis of the circadian pacemaker may be implicated in mental disorders. Abnormalities in sleep–wake rhythms, appetite, and social rhythms have been observed in depressive disorders, schizophrenia, bipolar disorder, anxiety disorders, seasonal affective disorder (SAD), and a variety of other CNS disorders (Lamont et al., 2007; McClung 2007). Recent studies show that disruption of one of the core proteins in the master circadian clock can trigger mania-like behaviors (Roybal et al., 2007) and human genetic studies associate polymorphic variations of the clock and clock-related genes with mood disorders (Benedetti et al., 2005a,b), and autism spectrum disorders (Bourgeron 2007) which suggest involvement of circadian genes in these disorders. The hypothesis that abnormalities in molecular clocks are implicated in psychiatric disorders is further supported by findings showing that stabilization of the biological clock function enhances efficacy of pharmacotherapies for psychiatric conditions. Despite the mounting evidence, the neurobiological bases of this connection are largely unknown.

The components of the molecular clock are widely expressed throughout the brain and the ability of these genes to switch between transcriptional activators and repressors suggest that they could orchestrate circadian control of neuronal gene expression and neuronal activity by influencing the function of neurotransmitters and receptors involved in regulation of emotion and cognition. For example, projections from the SCN to the locus coeruleus (LC) facilitate circadian regulation of noradrenergic activity and are important for transitions from focused attention to behavioral flexibility (Aston-Jones et al., 2001), contextual fear conditioning, circadian regulation of the sleep–wake cycle (Gonzales and Aston-Jones, 2006), and synaptic plasticity including long-term potentiation (Chaudhury et al., 2005; Chaudhury and Colwell, 2002). In adult rodents, activation of serotonin receptors, either the 5-HT1A, 5-HT2, or 5-HT7 receptor subtypes, resets the phase of the SCN circadian pacemaker (Tominaga et al., 1992; Gannon and Millan 2006; Ehlen et al., 2001; Duncan et al., 2004), whereas in prenatal rats, activation of dopamine receptors resets the developing circadian pacemaker (Shearman and Weaver 2001). Studies show that disturbances in the reciprocal relationship between molecular clocks and other neurotransmitter systems can lead to altered brain functions and behaviors. For example, animals with mutated Clock gene exhibit mania-like behaviors that can be rescued by expressing a functional Clock protein in the dopamine-rich ventral tegmental area-VTA (Roybal et al., 2007). Alterations in neuropeptide Y receptors produce anxiety-like phenotypes (Karl et al 2006) whereas exposure to stress alters expression of vasoactive intestinal peptide (VIP) mRNA and disrupts circadian rhythms (Handa et al., 2007). Mutant mice lacking the Clock analogue Npas2 display deficits in learning of cued and contextual fear paradigms, suggesting that Npas2 plays a role in the acquisition of specific types of memory (Garcia et al., 2000). These examples illustrate that the SCN-mediated
circadian clock outputs and the clock gene-mediated interaction with neurotransmitters and other neural processes is complex and likely plays an important role in the regulation of a wide range of behaviors including sleep, emotion, motivation, alertness, and cognition.

Despite the accumulating evidence linking alterations in circadian rhythms to behavioral disturbances and psychiatric diseases, a gap in understanding of the neurobiological mechanisms that underlie this interaction makes it challenging to determine whether circadian rhythms disturbances are the underlying causes of diseases or simply symptoms of the disease processes. To respond to these challenges and to encourage studies focusing on the mechanisms underlying the association between circadian rhythms with higher order brain functions we (a) assess current research findings and identify important questions relevant to the neurobiology of the interactions between circadian oscillators and the neural circuits implicated in higher brain function and behaviors of relevance to mental health, (b) evaluate how the most promising approaches could improve the understanding of how circadian rhythms regulate brain function and behavior under normal and pathological conditions, (c) identify current gap areas and challenges to advancing our knowledge of how disruptions in circadian rhythms and sleep may increase vulnerability for psychiatric disorders, and (d) consider possible avenues for translation of basic science discoveries in circadian biology to clinical settings with the goal to define possible avenues for translation of basic science discoveries in circadian biology to clinical settings with the goal to define risk factors, prevent or delay onset of mental illnesses, design diagnostic tools, and propose new therapeutic strategies for mental illnesses.

We combine a critical evaluation of literature with discussions of five major themes focusing on research questions and novel findings pertinent to (1) the impact of molecular clocks on physiology and behavior, (2) the interactions between circadian signals and cognitive functions, (3) the interface of circadian rhythms with sleep and its relevance to normal and abnormal behaviors, (4) a clinical perspective on the relationship between circadian rhythm abnormalities and affective disorders, and (5) the animal models of circadian rhythm abnormalities and mood disorders. We also discuss opportunities, gaps, and challenges in studying the association between disturbed circadian rhythms and psychiatric disorders and strategies for implementing knowledge drawn from basic science studies into clinical realm and vice versa.

2. Results

2.1. Impact of molecular clocks on physiology and behavior

A complex relationship among the symptoms of psychiatric illnesses, sleep, and circadian rhythm dysfunction has been identified. Traditionally, sleep disruption has been considered to be a symptom of several psychiatric disorders, including bipolar disorder, schizophrenia, major depression, and SAD as well as mood, anxiety, and substance use disorders (Benza, 1996). However, it remains possible that disordered sleep reflects impaired biological clock function which provokes the development and maintenance of psychiatric disorders in susceptible individuals (Mansour et al., 2006). It is critical to dissect the effects of clock genes on circadian organization and sleep disruption and understand their individual and synergistic contributions to mental disorders. Furthermore, many individuals at risk for mental disorders live in environments that have altered circadian rhythms including irregular sleep schedules, meal times, or other temporal constraints (Colten and Altevogt, 2006).

The SCN functions as the primary central circadian oscillator in mammals (Stephan and Zucker, 1972; Moore and Eichler, 1972). Output from the SCN is capable of producing sustained and synchronous cellular rhythmicity in both central and peripheral tissues, resulting in the temporal organization of molecular and behavioral rhythms throughout the body (Liu et al., 2007). Circadian dysfunction associated with psychiatric illnesses likely represents uncoupling of autonomous oscillators in the SCN or disruptions in the output from the SCN to other parts of the brain (Yang et al., 2008). Despite some promising early leads, sensitive and specific sleep biomarkers of psychiatric disorders have not been validated (Yang et al., 2008). Although it is difficult to observe cellular circadian dysfunction in neurons, a simple system may be necessary to untangle the complex interactions among the SCN, sleep, and mood. Fibroblasts are relatively easy to obtain and evaluate; thus, examination of the effects of genetic disturbances at the level of single cells could be linked to behavioral changes to reveal how intercellular coupling mechanisms are important for appropriate and robust circadian clock gene function (Welsh et al., 2004; Yang et al., 2008). Because intercellular coupling of circadian oscillators can compensate for genetic deficiencies in individual clock components, further understanding of the regulation of coupling could provide novel insight into the mechanisms of increasing the resistance to a variety of genetic disturbances that can perturb behavior. In one study, fibroblasts from bipolar patients and healthy individuals were examined for rhythmic expression patterns of core clock genes as well as mRNA expression levels of four kinases associated with clock function (Yang et al., 2008). Their results suggest that reduced amplitudes and overall expression levels of some circadian genes, and the decreased phosphorylation level of GSK3, may lead to dysregulation of downstream genes, which might account for some pathological features of bipolar disorder. Thus, the existence of rhythms in cultured fibroblasts and other tissues suggests their translational potential as peripheral markers for disturbances in circadian rhythms in psychiatric disorders.

Examination of the biological mechanisms underlying circadian clock-regulated behaviors can provide clues into how impaired circadian rhythms may lead to behavioral disruptions. In Drosophila, the regulation of sleep involves an interaction of the circadian system that controls the timing of sleep with a homeostatic system that regulates the need for sleep (Koh et al., 2008). Norepinephrine is important in regulating vertebrate sleep (Hunsley and Palmiter, 2004), whereas octopamine, an invertebrate homolog to norepinephrine (Roeder, 2005), appears important in regulating sleep as well as several other cognitive and affective responses in flies. Disruption of octopamine production through a variety of genetic and pharmacologic techniques results in increased...
sleep (Crocker and Sehgal, 2008). Furthermore, a large-scale, unbiased genetic screening identified a novel gene, sleepless (ss), that acts as a signaling molecule necessary for maintenance of baseline and rebound sleep in Drosophila (Koh et al., 2008). Loss of the SLEEPLESS protein reduced sleep by >80%, whereas reduced SLEEPLESS protein had little effect on baseline sleep but impaired rebound sleep. Elevated levels of SSS are required for sleep rebound in order to overcome the circadian-based morning waking drive. The analogs of these sleep genes in mammals await discovery, but they would likely be important in untangling the relative contribution of circadian disruption and sleep disturbances in psychiatric disorders. Importantly, this basic research has the potential to settle whether sleep disorders are the result or cause of psychiatric disorders.

The function of sleep remains unspecified, but down-regulation of specific metabolic processes has been hypothesized. Recently, the transcriptional coactivator PGC-1α has been proposed as a link between the mammalian circadian clock and energy metabolism (Liu et al., 2007). Additional evidence for the idea that circadian cycles may be driven by metabolic cycles includes the ubiquitous expression of oxidative-phosphorylation genes that oscillate in a circadian fashion in the SCN, the circadian clock-driven periodic expression of many metabolic genes, and the strong parallel between metabolic cycles and circadian cycles (Tu et al., 2005). The sleep–wake cycle likely reflects ancient cycles in light-dependent and dark-dependent biochemical processes. In budding yeast, the “charging” phase of the reduction/charging cycle of yeast may be an early homolog of sleep. Furthermore, evidence of circadian fluctuations of glycogen stores, 2-deoxyglucose uptake, and many oxidative-phosphorylation genes between sleep and wakefulness suggests that sleep–wake cycles may be regulated by fluctuating metabolic states that occur as a result of alternating levels of metabolic activity (Dudley et al., 2003). Because sleep might be needed as a resting and detoxifying phase in the brain following intense metabolic activity during wakefulness, the sleep–wake cycle and circadian rhythms of mammals may be governed by an intrinsic metabolic cycle (Tu et al., 2003; Tu and McKnight, 2006). Better understanding of the properties and regulatory mechanisms of the metabolic cycle will likely provide insight into the homeostatic nature of sleep and into cognitive and affective disturbances associated with genetic and physiological perturbations of circadian rhythms and sleep.

Taken together, these and other molecular approaches combined with additional development of model systems are necessary to identify novel mechanisms that could explain how circadian rhythms control behaviors under both normal and pathological conditions and untangle the contributions of circadian processes from sleep and psychiatric disorders.

2.2. Interactions between circadian signals and cognitive functions

Mood and affective disorders are associated with impairments in cognition, including deficits in attention and memory, which are exacerbated by aging (Jorm, 2000; Kumar et al., 2006). Both the endogenous circadian timing system and exposure to ambient light are known to influence cognition and affective state (Chaudhury and Colwell, 2002; Chen et al., 2008; Gonzalez and Aston-Jones, 2008; Hampp et al., 2008; Ruby et al., 2008). This section focuses on (1) the role of circadian signals in regulating attention, arousal, and memory; (2) the effect of seasonal changes in the daily lighting cycle (photoperiod) on memory and behaviors indicative of depression and anxiety; and (3) the effect of aging on the circadian timing system.

Depression is characterized not only by feelings of sadness and worthlessness but also by inertia, lethargy, and impaired cognition that is more prevalent in the elderly (Geda et al., 2006) (Jorm, 2000; Kumar et al., 2006). Cognition, including learning, memory, and executive function, requires alertness and the ability to appropriately maintain or change focus under various situations. The ability to learn and remember varies over the course of the day and has been shown under controlled conditions to exhibit bona fide circadian rhythms (Chaudhury and Colwell, 2002), i.e., ∼24-h rhythms that are endogenously generated and can be entrained by the ambient light–dark cycle. Disruptions of circadian rhythms, especially sleep–wake rhythms, are observed in all major forms of depression (McClung, 2007). Furthermore, as demonstrated first for SAD and later for other depressive disorders, bright light exposure can alleviate the symptoms or severity of depression in many patients (Terman and Terman, 2005). The antidepressant effect of bright light might be mediated by its robust and well-known effects on the circadian clock or by other mechanisms, as described below.

What are the mechanisms by which the circadian timing system regulates cognition, memory, and mood? A variety of neuroanatomical, neurophysiological, molecular, and neurochemical mechanisms have been revealed. The neuroanatomical circuit mediating circadian regulation of arousal is a multisynaptic pathway between the SCN and the noradrenergic neurons of the LC (Aston-Jones et al., 2001; Deurvielher and Semba, 2005). The behavioral state of arousal and wakefulness is induced by stimulation of the frontal cortex by noradrenergic neurotransmission arising from the LC (Aston-Jones and Bloom, 1981; Gonzalez and Aston-Jones, 2006). Decreases in noradrenergic activity, as well as serotonergic activity, are associated with depression. In rats, prolonged light deprivation leads to loss of noradrenergic fibers in the frontal cortex, decreased amplitude of the sleep–wake rhythms, and delayed onset of activity periods (Gonzalez and Aston-Jones, 2006). In addition, long-term light deprivation induces apoptosis of LC noradrenergic neurons and increases immobility in the forced swim test, an indicator of depressive-like condition; treatment with the antidepressant, desipramine, alleviates both of these effects (Gonzalez and Aston-Jones, 2008). These profound effects of light deprivation may help to explain the mechanisms underlying the amelioration of depression by bright light.

How does light information reach the LC, which is not known to exhibit photoreceptors or direct retinal projections? As shown by neuroanatomical tract tracing as well as lesion studies, the neurons in the SCN, which receives retinal input, project to the dorsomedial hypothalamus (DMH), which in turn projects to the LC (Aston-Jones et al., 2001; Deurvielher and Semba, 2005). The functional importance of this circuit was demonstrated by the findings that lesions of the DMH
eliminate the circadian rhythm in LC neuronal activity, whereas lesions of the LC decrease the amplitude of circadian rhythms of slow wave activity in the cortex (Aston-Jones et al., 2001). Orexin-containing neurons are critical components of the pathway from the DMH to the LC (Gompf and Aston-Jones, 2008; Horvath et al., 1999).

Circadian rhythms not only govern sleep–wake cycles but also rhythms in cognitive processes including subjective alertness, mathematical ability, and memory. During waking, there are transitions between focused attention and behavioral flexibility that are accommodated by a multifunctional system in the LC. The LC changes its activity between phasic or tonic modes (Aston-Jones and Cohen, 2005; Usher et al., 1999). During the phasic mode, the characteristics of LC neuronal activity include a moderate baseline firing rate, large phasic responses, and transient increases in gain after task-relevant events, all of which favor task-focused behavior. In contrast, during the tonic mode, LC neuronal activity is characterized by a higher baseline firing rate, diminished or absent phasic responses to task-relevant events, and indiscriminate increases in gain, including increased responsiveness to noise. The characteristics of the tonic mode favor distractibility and exploration. It remains to be determined if the circadian neural circuit innervating the LC influences the expression of the tonic or phasic mode, or if affective disorders are associated with over- or under-expression of either of these modes.

As well as alertness and arousal, the circadian timing system regulates learning and memory. For example, circadian rhythms in contextual fear conditioning and synaptic plasticity (long-term potentiation, LTP) have been reported in mice (Chaudhury et al., 2005; Chaudhury and Colwell, 2002). Three treatments that disrupt circadian rhythms, i.e., mutation of the Period2 (Per2) gene, mutation of the gene encoding VIP, and exposure to rapidly changing photoperiods lead to deficits in fear conditioning recall in the absence of any detectable changes in acquisition of fear conditioning (Chaudhury et al., 2008). In confirmation of these findings in mice, studies in Siberian hamsters also show that alterations in the photoperiod sometimes lead to loss of circadian rhythmicity and concomitant loss of recall of a novel object (Ruby et al., 2008). Although the VIP-deficient mice exhibit lower levels of recall, they retain circadian rhythms of recall, even in the absence of circadian rhythms in wheel running behavior. These rhythms in recall are likely to be caused by circadian oscillations in some brain region other than the SCN, perhaps the hippocampus, in view of its well-known role in memory processes and its circadian expression of Per2 in VIP-deficient, behaviorally arrhythmic, mice (Chaudhury et al., 2008). Whether circadian oscillations in the hippocampus are necessary for the expression of circadian rhythms in recall, and if so, how these oscillations might affect memory processes, is not yet known.

The circadian timing system most likely affects memory, cognitive function, and behavior through a variety of mechanisms. Because some psychopathologies are exacerbated by changes in season (Morera and Abreu, 2006), one possibility concerns the role of the circadian rhythms in mediating photoperiodically induced, seasonal responses. Seasonal changes in day-length (photoperiod) induce many physiological and behavioral changes in animals living at temperate latitudes, including humans. Photoperiod regulates the circadian rhythm in pineal secretion of melatonin, which in turn regulates seasonal changes in reproduction, metabolism, and behavior (Goldman and Nelson, 1993). Melatonin not only mediates seasonal changes but also affects influences circadian rhythms and sleep (for review, see Dubocovich, 2007). In rodents, such as white-footed mice, exposure to a short-day, winter-like photoperiod impairs spatial learning and alters hippocampal plasticity, such as dendritic spine density and decreased LTP in the CA1 (Pyter et al., 2008). Furthermore, short-day photoperiod exposure and water maze experience appear to interact to affect neurogenesis the hippocampus.

As well as altering cognition and its neural substrates, short-day photoperiod exposure influences affective state. For example, short-day housed male Siberian hamsters exhibit elevated anxiety-like and depressive-like behaviors (Prendergast and Nelson, 2005). These behaviors are influenced not only by acute short-day photoperiod exposure but also by prenatal melatonin exposure in utero, suggesting that photoperiodic exposure of the mother during gestation may organize the developing brain via exposure to the mother’s melatonin rhythms, influencing subsequent adult affective responses (Workman et al., 2008). It is also interesting to note that the short-day photoperiod induction of anxiety- and depressive-like behaviors is associated with increased serotonin transport in the midbrain, consistent with the therapeutic use of selective serotonin re-uptake inhibitors (SSRIs) to combat anxiety and depression in humans.

In humans, the incidence of depression and impairments in cognitive function, most notably spatial memory, are higher among the elderly (Geda et al., 2006; Jorm, 2000; Kumar et al., 2006). Interestingly, aging is also associated with decrements in the circadian rhythms, including decreased amplitude, fragmentation or loss of rhythms, alterations in entrainment, and decreased sensitivity to phase resetting signals, including light and nonphotic signals, e.g., benzodiazepines and serotonergic drugs (reviewed in Hofman and Swad, 2006; Duncan, 2007). Reports that selective serotonin denervation of the hamster SCN mimics some of these aging effects (Meyer-Bernstein and Morin, 1998) led to the hypothesis that aging might be associated with decreased serotonergic neurotransmission in the SCN. Indeed, in the hamster SCN, aging is accompanied by increases in both the serotonin terminal autoreceptors, 5-HT1B receptors, and the serotonin transporter (SERT) binding sites, alterations that are likely to decrease SCN extracellular serotonin levels (Duncan et al., 2000). Aging also alters serotonin neurotransmission in a midbrain region, the dorsal raphe nucleus (DRN), which communicates indirectly with the SCN as well as with many forebrain regions. Aging selectively decreases 5-HT1B receptors in the hamster DRN, strongly attenuating circadian phase shifts induced by microinjection of serotonergic agonists in this region (Duncan et al., 1999, 2004). The age-related loss of 5-HT1B receptors in the DRN may represent down-regulation caused by decreased SERT binding sites (Duncan and Hensler, 2002), which in turn may help to elucidate the reduced efficacy of SSRIs in alleviating depression in the elderly.

In summary, circadian rhythms and ambient photoperiod influence cognition and affective behavior through multiple
mechanisms, including regulation of noradrenergic innervation of the cortex, clock gene expression in the SCN and hippocampus, dendritic spine density, and serotonin transport. Animals exhibiting clock gene mutations, or animals exposed to various photoperiods, may be used as experimental models for probing the interaction of circadian signals with cognition and affective state. Application of chronobiological principles to the management of psychophatophysiological conditions has led to the development of novel nonpharmacological therapies (e.g., light exposure and sleep deprivation) as well as novel drugs (e.g., ramelteon) and will likely lead to others in the future.

2.3. Interface of circadian rhythms with sleep and its relevance to normal and abnormal behaviors

Sleep is one of the most important behaviors influenced by the circadian system, and specific changes in sleep patterns, as well as circadian rhythms, have been described in a number of neuropsychiatric disorders, most notably mood disorders. Recent work suggests that relationships between circadian rhythms and sleep may contribute to normal and abnormal behaviors.

Although circadian rhythms certainly influence the timing of sleep and wakefulness across the day, a number of other factors regulate patterns of sleep, including developmental and environmental effects. Perhaps the most important determinant of sleep behavior, however, is the homeostatic drive for sleep; the longer an organism is awake, the greater the pressure to sleep. The homeostatic sleep process is thought to regulate the amount of sleep obtained and is likely related to the function of sleep; knowing why sleep is necessary for the brain is critical to understanding relationships between sleep and circadian rhythms. Tononi and Cirelli (2003) have proposed that sleep reverses the "costs" of being awake, which accrue from the build-up of synaptic strength in the brain through the process of long-term potentiation (LTP) and include increased energy utilization, increased neuropil density, increased need for cellular supplies, and saturation of the ability to learn. Prolonged waking decreases the ability to induce further LTP in various models, which in turn should inhibit learning (Vyazovskiy et al., 2008); this is supported by studies in normal humans demonstrating that sleep deprivation impairs the ability to acquire new memories (Yoo et al., 2007).

The homeostatic drive for sleep, which increases during normal wakefulness and especially during sleep deprivation (prolonged and enforced wakefulness), is reflected by slow wave activity, defined as power spectral activity between 1 and 4 Hz during non-rapid eye movement [NREM] sleep. Recent evidence suggests that slow wave activity is also an indicator of synaptic strength in the brain (Esser et al., 2007; Vyazovskiy et al., 2007). At the beginning of the sleep period, slow wave amplitude is high and the average slope of individual slow waves is steep, indicating high overall synaptic strength, but at the end of the night, both slope and amplitude are decreased as synapses weaken. That slow wave activity during sleep is reflective of brain activity during wakefulness has been demonstrated in a number of ways. Slow wave activity can be increased locally as a result of specific learning tasks; a motor learning task that is known to activate parietal cortex led to increased slow wave activity in the same region during sleep following performance of the task (Huber et al., 2004). Slow wave activity during sleep can also be decreased locally in the brain; immobilizing a limb, for example, led to decreased slow wave activity in contralateral sensorimotor cortex during subsequent sleep (Huber et al., 2006).

The relationship of LTP during waking to increased production of slow waves in sleep is likely relevant for depression, in that most effective antidepressants increase expression of plasticity-related genes (reviewed in Duman, 2002; Payne et al., 2002) much like sleep deprivation (Cirelli et al., 2004), although on a longer time course. Thus, an increase in synaptic potentiation may explain the antidepressant effects of acute sleep deprivation, and synaptic downscaling by slow waves during sleep the rapid reversal of these antidepressant effects by even short bouts of recovery sleep. Furthermore, depression is characterized by decrements in slow wave sleep and slow wave activity, suggesting the possibility that abnormalities in sleep homeostasis may somehow be related to depression.

Potential mechanistic links between the circadian system and homeostatic regulation of sleep include the Period (Per) genes, named for their role in determining the duration of the period of the circadian rhythm. Individuals with a variable-number tandem-repeat polymorphism of Per3 display elevated slow wave sleep and slow wave activity and more severe cognitive decrements in response to sleep deprivation than unaffected individuals (Viola et al., 2007). However, circadian rhythms, insofar as they have been assessed, do not seem to be abnormal in these individuals.

Developmental aspects of sleep and circadian rhythms are likely to have profound impact on brain function and mental health. Sleep and circadian rhythm abnormalities in children and adolescents may be risk factors for the development of psychiatric disorders and have been implicated in depression and bipolar disorder (Harvey et al 2006), attention-deficit disorder (Owens 2008), and autism (Bourgeron 2007). However, despite the possible link between sleep abnormalities during childhood and psychiatric disorders, the role of sleep in the regulation of higher order brain functions and in defining transitional periods in the development of brain functions that may be most vulnerable to changes in sleep have been less investigated. It would be worthwhile addressing whether the dramatic changes in sleep patterns and synaptic pruning seen in adolescence simply reflect normal developmental changes in gray and white matter development, or whether they are causally related, thus reflecting the ongoing process in gray and white matter development.

Both homeostatic and circadian aspects of sleep regulation show profound changes during development, although it is not clear whether these are independent of each other or if developing circadian and homeostatic sleep regulatory mechanisms interact. For example, significant maturational changes in sleep patterns occur after birth in mammals, including development of the typical sleep waveforms (e.g., slow waves and sleep spindles), as well as the emergence of circadian rhythms. Studies in rats have shown that although...
delta rhythm and other typical EEG features of quiet (NREM) and active (REM) sleep do not appear until postnatal day 11, the general organization of cycling between quiet and active sleep can be detected at least several days earlier, and remains stable (Seelke and Blumberg, 2008). The overall temporal organization of sleep and waking episodes, however, changes across the postnatal period. Adult mammals, including rats, cats, and humans, display brief waking bouts during the sleep period that show a power law distribution, whereas sleep bout durations are exponentially distributed (Lo et al., 2004). In studies of developing rats, however, at postnatal day 2, both sleep and waking bout durations distribute in an exponential pattern, and waking bout durations do not switch to the adult, power law distribution until about postnatal day 15 (Blumberg et al., 2005). Although the mechanistic basis for the organization of sleep–waking patterns across the sleep period is not known, the consistency of these patterns across species of adult mammals suggests similarities in the underlying neural control of sleep organization, which may include both homeostatic and circadian features.

Age and brain development affect slow wave activity in sleep; during childhood, when brain synaptic density is greatest, slow waves show the highest slopes and the greatest activity. During adolescence, slow wave activity declines (Jenni and Carskadon, 2004), possibly in relation to the synaptic pruning that occurs during this period of development. Moreover, the rate of accumulation of sleep pressure as indicated by slow wave activity is more rapid in children than in adolescents (Jenni et al., 2005).

Circadian rhythms are likely expressed and functional earlier than previously thought, although their development may be shaped by early environmental influences. In developing rats, like other mammals, circadian regulation of sleep starts to emerge after birth. However, there is some evidence that suggests that visual input to the SCN is necessary for normal circadian development. Norway rats enucleated at postnatal day 3 showed a pattern of increased waking during subjective day when tested at postnatal days 21–35, which is opposite the normal pattern of increased waking during subjective night (this species is nocturnal) that typically develops by this time in normal animals, sham operated animals and rats enucleated at postnatal day 11 (Gall et al., 2008). However, regardless of the time of the lesion, the switch from exponential to power law distribution of waking behavior developed normally.

Hormonal influences are also important for development of sleep cycles. Puberty may be associated with a lengthening of the intrinsic period of the circadian clock (Carskadon et al., 2004). Studies in degus, a diurnal rodent, show that modulation of the circadian system in adolescence may be related to puberty because the progressive delay in the onset of activity following lights on that normally occurs during adolescence does not occur in animals gonadectomized prior to puberty (Hummer et al., 2007). Interestingly, the phase delay in adolescent humans and rodents reverses in young adulthood. As noted earlier, human adolescence is also associated with a decrease in slow wave sleep, and it is possible that the changes in both homeostatic sleep processes and circadian rhythms could contribute to the tendency for adolescents to show delayed sleep phase.

Adolescence is also a time associated with sleep deprivation, more so in industrialized societies, resulting from delayed bed times and early school start times. Those with greater tendency to delay circadian rhythms in adolescence may be more likely to become sleep restricted. Epidemiological evidence suggests that sleep-deprived teens are more likely to develop depressive symptoms (Fredriksen et al., 2004), and that teens who reported shorter sleep duration were more likely to engage in suicidal behavior (Liu, 2004). In rodents, chronic sleep restriction results in decreased sensitivity of 5HT1A receptors, and although these experiments were conducted in adult animals, they suggest that sleep loss can affect neural systems involved in mood and behavior as well as in the regulation of circadian rhythms (Novati et al., 2008).

Seasonal sleep and behavioral patterns may be relevant for mood disorders, particularly neuropsychiatric bipolar disorder. Although relatively little research has been conducted to examine seasonal influences in normal or pathological human states, there is some evidence for increased seasonality in bipolar patients. Bouts of depression are more common during the fall and winter, and peaks of mania tend to occur in the spring and summer. In comparison to unaffected twins or healthy individuals, bipolar patients reported greater seasonal variation in sleep length and mood (Hakkarainen et al., 2003; Shin et al., 2005; Wehr et al., 2001). Circadian and/or seasonal rhythm abnormalities may be a core feature in some patients with mood disorders and provide an opportunity for identification of at-risk individuals and/or targets for therapeutic interventions.

Seasons are a major environmental influence on both circadian and homeostatic patterns of sleep regulation. One of the most dramatic examples of seasonally related sleep changes is the white-crowned sparrow (Zonotrichia leucophrys gambelii), a songbird that migrates between California and Alaska. In captivity, these birds undergo periods of migratory restlessness during times of year when they would normally be migrating. Sleep EEG studies have shown that they decrease their overall sleep time by almost 2/3 during migratory restlessness in comparison to their winter, nonmigratory condition, without showing typical behavioral effects of sleep deprivation (Rattenborg et al., 2004). In contrast to the effect of sleep deprivation, the migratory state to increase motivation to work for food reward in a repeated acquisition task. White-crowned sparrows show homeostatic regulation of sleep (i.e., increased slow wave activity) in response to sleep deprivation, as well as similar patterns of gene expression to mammals in relation to sleep and sleep deprivation (Jones et al., 2008a,b), suggesting that seasonal variation in sleep amount may be due to changes in homeostatic and, possibly, circadian regulation of sleep.

Clearly there is a need for longitudinal human studies to understand normal and abnormal patterns of seasonal and circadian rhythms in humans, including gender effects on these rhythms. It is also not known whether circadian and seasonal rhythms are controlled by similar mechanisms and how they might interact. The effects of environment on development of rhythms, particularly during childhood and adolescence, is another critical area for investigation, as factors that contribute to abnormal development, such as
light exposure and sleep deprivation, may permanently alter brain systems involved in regulation of behavior.

Finally, there are promising avenues for improved diagnosis of neuropsychiatric disorders and identification of individuals at risk using new sleep technologies. For example, using high-density (256-channel) EEG, it is possible to determine the sources and traveling pathways of individual slow waves. Initial analyses of patterns of slow wave origin and spread across the cortex show local abnormalities in patients with strokes (Murphy et al., 2009), and in topography of slow wave activity in depression (Benca, Tononi, and Peterson, unpublished observations). More sophisticated topographical analysis of sleep-related waveforms may prove useful in determining patients at risk for a variety of illnesses. For example, over 90% of schizophrenic subjects show a dramatic reduction in sleep spindles, suggesting dysfunction in the reticular nucleus of the thalamus (Ferrarelli et al., 2007). If specific sleep EEG “fingerprints” for neuropsychiatric disorders can be determined, they may provide an opportunity to identify at-risk individuals.

2.4. Circadian rhythm abnormalities and affective disorders—clinical perspective

Data on the influence of clock genes and circadian rhythm abnormalities on psychopathology and treatment response are relatively sparse in humans but several major findings have emerged including those suggesting that psychosocial interventions that stabilize sleep–wake and other daily routines may have protective effects.

Total sleep deprivation, especially in combination with other chronobiological interventions, such as light therapy, is associated with improved treatment response, especially in bipolar depression (Benedetti et al., 2005a,b; Colombo et al., 2000; Wu et al., 2009). In contrast, light deprivation and increased sleep may be therapeutic for mania (Barbini et al., 2005). Polymorphisms of clock genes such as CLOCK, Per3, and GSK3-β can influence both the individual activity–rest rhythm and core characteristics of bipolar illness such as age at onset, recurrence of illness episodes, insomnia, and response to mood stabilizers (Benedetti et al., 2008; Benedetti et al., 2003a, b). Furthermore, the relationship between the psychopathological features of the illness and its lifetime development is also influenced by polymorphisms in the promoter region of the 5-HT transporter gene (Beaulieu et al., 2008; Benedetti et al., 2003a,b, 1999) suggesting that there is a two-way interaction between the individual features of clock machinery and monoaminergic systems. In order to elucidate the mechanisms of the apparent sensitivity to light in bipolar and depressed patients, it would be important to carry out multi-level interdisciplinary research studies including the interaction of the 5-HT transporter with clock genes, long-term changes in neural circuits, and comparison of the underlying mechanisms with those of clinically used drugs for these disorders.

Further support for the circadian influences on therapeutic outcomes in bipolar disorder is demonstrated by both short- and long-term studies with interpersonal and social rhythm therapy. This intervention is based on the theory that individuals with bipolar disorders have vulnerable circadian systems and that more regular daily routines can serve to strengthen the circadian pacemakers in such individual leaving them less vulnerable to new episodes of illness. These studies have shown that stabilization of social routines (including sleep–wake and activity rhythms with a presumed effect on endogenous circadian rhythms) is associated with more rapid recovery from bipolar depression (Miklowitz et al., 2007), has a significant prophylactic effect against new episodes of mania and depression (Frank et al., 2005), and is associated with significantly more rapid improvement in occupational functioning (Frank et al., 2005, 2008; Miklowitz et al., 2007). Prospective clinical studies of actual circadian function in patients treated with and without a social rhythm intervention offer promise of a better understanding of these relationships. Preliminary studies of youth at risk for bipolar disorder by virtue of having a first degree relative with the illness suggest that the presumed vulnerability in circadian function is already present in asymptomatic high-risk youth (Frank, unpublished observations).

A less well-known clinical condition, night eating syndrome (Stunkard et al., 1955), provides another opportunity to examine a psychopathological syndrome in relation to potential circadian rhythm disruption. The core criteria of evening hyperphagia, associated with nighttime awakening and ingestion, are associated with definite behavioral and hormonal phase delays (Allison et al., 2005; Birketvedt et al., 1999; O’Reardon et al., 2004). Treatment with SSRIs restores the circadian rhythm and it appears to be effective in controlling the episodes of nocturnal eating (Miyaoka et al., 2003; O’Reardon et al., 2005; Stunkard et al., 2006). Such interventions suggest possible relationships with 5-HT transporter changes, supported by SPECT studies (Lundgren et al., 2008).

It would be useful to carry out additional pre-clinical studies that include animal models of circadian genes dysfunction as well as clinical studies that further explore the relation between circadian dysfunction and pathological states. Prospective studies should examine circadian function and disruption in patients with mood disorders, early in the course of their illness, and in youth at risk for bipolar disorder. Comparisons of the effects of therapeutic strategies, including mood stabilizers (e.g., lithium) and social rhythm therapy, not only on the symptoms of bipolar illness but also on the expression of circadian rhythms and sleep–wake cycles, would be informative. There is a need for mechanistic studies to elucidate the neural basis of social rhythm therapy in bipolar disorder and other therapeutic interventions with presumed effects on the circadian system, the consequences of circadian rhythms disruption on mental health, and the interaction between clock gene polymorphisms and changes in emotion and cognition. It would also be important to assess the circadian rhythms in neurotransmitter systems in patients with mood disorders and the patterns of mood variation (including circadian vs. homeostatic components) in both unipolar and bipolar patients. Finally, model systems for studying the mania–depression–euthymia switch that occurs in bipolar disorder would facilitate studies beyond the current models that only focus on steady-state conditions.
2.5. Pre-clinical models of circadian rhythm abnormalities and mood disorders

It is becoming increasingly apparent that circadian rhythms are central in the pathophysiology of several diseases, such as mood disorders, sleep disorders, and metabolic diseases. Individuals with bipolar disorder, major depression, and SAD all have major rhythm disruptions. Furthermore, depressive or manic episodes are often precipitated by changes to the normal sleep–wake schedule. Metabolic disorders also appear to be linked to both mood disorders and changes in circadian rhythms. Indeed recent reports suggest that sleep problems, mood problems, and obesity are “interacting epidemics” (Laposky et al., 2008). Over the last decade, many of the genes responsible for regulating circadian rhythms have been identified. This has allowed exploration of the mechanisms by which circadian genes and rhythms are involved in regulating mood and metabolism.

In recent years, ethynitrosourea (ENU) mutagenesis has been used in mice to discover genes involved in sleep and circadian rhythms. This technique has lead to the identification of a number of mutations that produce abnormalities in circadian rhythms, sleep time, and rebound. This includes the identification of the Clock gene which is one of the central components of the circadian machinery (King et al., 1997). Interestingly, some of these circadian and sleep mutants have abnormalities in additional neurobehavioral measures indicative of anxiety and mood-related changes. In addition, mice that have a mutation in the Clock gene spend less time in all phases of sleep and have a number of symptoms indicative of metabolic disorder (Naylor et al., 2000; Turek et al., 2005). This includes weight gain, particularly on a high fat diet, and changes in the expression of feeding-related hormones and peptides in the body. In concert with these findings, simply feeding mice a high fat diet alters the circadian period and attenuates the diurnal pattern of feeding behavior (Kohsaka et al., 2007). This could be important for the development of a number of obesity-related disorders.

Some of the most pronounced rhythm disruptions are observed in bipolar patients and altered sleep–wake patterns are fundamental to the diagnosis. Mice with a mutation in the Clock gene have a behavioral profile that is strikingly similar to human mania (McClung et al., 2005; Roybal et al., 2007). This includes hyperactivity, lowered depression-like behavior, greater risk taking behavior, an increase in the preference for sucrose and cocaine, and an increase in goal-directed behavior resulting in intracranial self-stimulation. Furthermore, the majority of these phenotypes are reversed when animals are treated chronically with the mood stabilizer, lithium (Roybal et al., 2007). Altered dopaminergic signaling in the reward circuit of these mice was suspected and it was verified that Clock mutants display increased dopaminergic cell firing and bursting in the VTA (McClung et al., 2005). To determine whether CLOCK expression in the VTA is important in regulating mood-related behavior, viral-mediated gene transfer was used to place a functional Clock gene back into the VTA of the Clock mutant mice. This was able to rescue their hyperactivity and anxiety-related behavioral abnormalities (Roybal et al., 2007). CLOCK acts as a transcription factor, and a microarray analysis identified a number of potential target genes of CLOCK in the VTA which are important regulators of dopaminergic activity (McClung et al., 2005). These mice should facilitate elucidation of mechanisms by which CLOCK regulates dopaminergic activity and behavior (McClung et al., 2005). These studies will also help to determine the biological abnormalities that underlie bipolar disorder including the specific role for circadian genes in the development of this disease.

The Clock mutant mice are not the only mice that have a behavioral profile similar to human mania. By determining what additional genes contribute to a manic-like phenotype, we may be able to determine more specifically how the circadian system interacts with other systems to produce mood changes. In addition to the dopaminergic system, the glutamatergic system has been suggested as a possible regulator of manic-like behavior. Indeed, Glutamate receptor 6 (GluR6) knockout mice are hyperactive, have an increased response to amphetamine, have low anxiety-related behaviors, and have lower depression-like behavior (Shaltiel et al., 2008). These mice are also more aggressive than wild type mice. Lithium treatment was able to reduce their hyperactivity, increase anxiety, and reduce their aggressive behavior. However, interestingly, lithium further reduced their immobility in the forced swim test (a measure of depression-like behavior) instead of bringing the mice back towards wild type levels as seen with the Clock mutants. Lithium treatment had no effect on levels of GluR5 in the hippocampus of the GluR6 knockout animals suggesting that this is not the mechanism by which lithium is restoring normal activity and anxiety-related behavior to these mice (Shaltiel et al., 2008). It is unclear whether GluR6 is involved in the regulation of circadian rhythms, but it is interesting that the GluR6 knockouts share similar phenotypes with the Clock mutants. It is possible that GluR6 and Clock regulate each other in some way, or that the loss of both of these genes leads to common effects on neuronal activity.

Because circadian rhythm abnormalities may contribute to the development of mood and metabolic disorders, researchers are trying to identify drugs that will alter circadian rhythms and perhaps restore normal rhythmicity when rhythms are compromised. Bright light therapy and melatonin therapy have been used extensively to treat SAD. Both are effective at shifting circadian rhythms either forward or backward depending upon the time of day in which they are administered. A recent study reported that the proper shifting of rhythms in individual SAD patients is necessary for therapeutic effects suggesting a real circadian basis for SAD (Lewy et al., 2006). Patients with bipolar and sleep disorders may also benefit from proper rhythm alignment. Recent studies find that casein kinase 1 epsilon/delta may be an interesting target for drug design for rhythm modifications. Casein kinase 1ε/δ phosphorylates the period and cryptochrome proteins, leading to control of circadian timing. A compound originally developed by Pfizer, PF-670462, is a >30-fold selective inhibitor of CK1ε/δ over other kinases (Badura et al., 2007). This compound leads to dose-dependent phase delays in locomotor activity in both nocturnal and diurnal species. It is unclear whether or not this drug will be useful in the treatment of disease, and this will be determined in further testing. Other studies are exploring the potential for
circadian phase shifting through alterations in the signaling by the melanopsin-containing retinal ganglion cells to the SCN; such studies may provide alternative ways to alter the phase of circadian rhythms.

In summary, animal models can be useful in identifying genes that are involved in the regulation of complex behaviors and psychiatric disorders. Furthermore, the circadian genes appear to be involved in the regulation of mood, sleep, and metabolism, perhaps through their functions outside of the SCN. If these diseases are caused by disrupted rhythms, it would be useful to engineer drugs that can restore these rhythms and treat the disorder. This is an exciting time in the circadian and affective disorder fields and there is no doubt that more promising work lies ahead.

3. Discussion

Here we present an integrated perspective on pre-clinical and clinical studies and research opportunities pertinent to neurobiological mechanisms that govern the association between circadian rhythms with higher order brain functions and behaviors of relevance to mental health. Several research areas were identified that could advance understanding of this association and elucidate at the mechanistic level how disturbances in circadian rhythms might be responsible for the symptoms of psychiatric disorders.

The ability of circadian oscillators in the SCN to produce sustained and synchronous cellular rhythmicity in both central and peripheral tissues and to produce efficient integration of molecular with behavioral rhythms throughout the body indicates the importance of using systems level and integrative approaches to elucidate the neural bases underlying the role of circadian oscillators in learning and memory, attention, arousal, affect, anxiety, and motivation under both normal and pathological conditions. Better understanding of the role of circadian regulation of complex behaviors may be aided by the development of biomarkers that reflect disturbances in brain circadian rhythms and mental health relevant behaviors. For instance, cultured human fibroblasts derived from biopsies express sustained circadian rhythms similar to cultured SCN neurons from rodents. Thus, studies examining their translational potential as biomarkers may reveal mechanisms of circadian rhythm disturbances in psychiatric disorders. Concurrent studies of circadian rhythms in fibroblasts and genetic polymorphisms related to circadian control may facilitate comparison between individuals with bipolar disorder and those at risk for the illness.

It has been hypothesized that cyclic changes in metabolic states of cells may play a role in the regulation of biological rhythms and sleep. The interplay between neuronal metabolic cycles and circadian rhythms may be important for neural plasticity and learning and memory processes. It would be interesting to explore whether this interaction regulates sleep–wake cycle and functioning of neural systems early and throughout development, especially during key transitional phases associated with marked changes in brain function and behavior.

There is a pressing need for more in depth studies addressing the gaps between neural circuits and mental health relevant behaviors. For instance, it would be pertinent to elucidate whether neuronal projections from the SCN to LC mediate changes in the amplitude of circadian rhythms, and whether this circuitry plays a role in circadian regulation of arousal, affect, and cognitive function. Additional research on this circuitry is warranted to elucidate transitional changes between focused attention and behavioral flexibility that are accommodated by a multifunctional system in the LC. It will be also important to explore further the interaction of the SCN with other complex networks including the hippocampus, the dorsal raphe, and the amygdala in order to determine whether circadian oscillations in these regions are necessary for the expression of circadian rhythms in memory recall process, fear learning and extinction, and anxiety and depressive symptoms. Studies on the interaction between the CLOCK protein and the VTA dopaminergic neurons provide an excellent model for studying mania-like phenotypes. Because in the VTA of the Clock mutants CLOCK might be implicated in regulation of locomotor activity, dopaminergic neuron activity, and anxiety-like behaviors, examination of the clock network interaction with monoaminergic neural circuits will facilitate defining of the brain systems underlying regulation of mood and complex behaviors. In addition, a more systematic characterization of the Clock mutants and other circadian mutants in both sexes is likely to facilitate discovery of novel behavioral phenotypes related to clock genes and to uncover the role of dysfunctional clock genes in altered emotional behaviors.

More studies are needed to elucidate the role, regulatory factors, and underlying genetic and cellular mechanisms of sleep and circadian rhythms in the context of higher order brain functions during transitional periods of development, across species, sexes, and throughout the lifespan. Novel studies demonstrating a tight relationship between cortical plasticity and slow wave sleep activity have tremendously improved understanding of the role of sleep in neuronal plasticity, emotion, learning, and memory. Further studies are needed to elucidate how developmental changes in sleep and circadian rhythms may be critical for the regulation of higher order brain functions including cognition, emotion, and affect. It would be also important to further understand the role of sleep and circadian rhythms in defining critical periods in the development of these higher order brain functions that may be most sensitive to changes in rhythms and sleep.

These also indicate the importance of determining the mechanisms underlying interaction of circadian clock genes with species-typical environments to elucidate the complex relationships between genetics, environment, and neurodevelopment in context of understanding brain function and mental disorders. Understanding these factors should facilitate discovery of circadian rhythm/sleep-specific physiological markers that can be utilized to identify high levels of risk for mental disorders.

Studies investigating how disruptions in social zeitgebers produce disturbances in the circadian rhythms that may increase vulnerability to mood disorders warrant more integrative and systems level approaches. For example, it would be important to investigate whether underlying mechanisms of dysfunctions in biological rhythms are linked to disruptions in the clock network that synchronizes phase
relationship between sleep and higher order brain functions. Treatments for bipolar disorder that combine pharmacotherapy with interpersonal and social rhythm therapy demonstrate that social rhythm stabilization speeds recovery from acute bipolar depression and delays the recurrence of both manic and depressive episodes. Understanding neurobiological underpinnings of the effects of social zeitgebers on mood and behavior would shed light on how stabilization of social rhythms may be relevant for those at risk for bipolar disorder and how it may improve outcomes in those individuals already diagnosed with this disease.

Advances in human genetic studies that show associations of polymorphic variations of the core circadian clock genes and clock-related genes with mood and sleep disorders have opened a new area in circadian biology. For example, a single nucleotide polymorphism—SNP in the 3’ flanking region of the Clock gene influences diurnal preference in healthy human subjects and causes sleep phase delay and insomnia in patients diagnosed with bipolar disorders while GSK3-β gene polymorphisms influence responses to lithium treatment. It is important to elucidate the mechanisms underlying these associations between genetic polymorphisms and mood disorders. Furthermore, the interplay between the circadian clock and serotonin transporters appears to play a role in positive effects of total sleep deprivation in depressed individuals as well as positive effects of light exposure in bipolar patients. To elucidate the mechanisms of the apparent sensitivity to light in bipolar and depressed patients, it would be necessary to carry out multi-level interdisciplinary research studies investigating clock gene polymorphisms associated with affective disorders. These studies would be complemented by studies examining the interaction of clock genes with the serotonin transporter and long-term changes in neural circuits that are implicated in affective disorders. Finally, it would be pertinent to carry out longitudinal studies that define specific circadian sleep–wake phenotypes and correlate these with their corresponding genotypes in order to clarify how this interaction might influence circadian patterns of cognitive function and emotion regulation.

In summary, we review here several important questions, strengths, and gap areas relevant to research on the neurobiological underpinnings of the circadian rhythms interaction with higher order brain function and behavior. The review discusses promising research directions and strategies for expanding basic, translational, and clinical studies on circadian rhythms to help bridge the gaps between genes, circuits, and behavior. Studies focusing on the interaction between biological clocks and neural circuits considering differences between normal and abnormal conditions, diagnostic subgroups, sex and gender, and gene–environment development interactions are likely to facilitate translation of basic science knowledge on biological clocks into the clinical arena and to improve understanding of how disturbances in this relationship contribute to psychiatric disorders.

Acknowledgments

We thank Dr. Kevin Quinn (NIMH) and Dr. Beth-Anne Sieber (NINDS) for insightful discussions of the manuscript and Ms. Laura Fonken (Ohio State University) and Ms. April Harrison (NIMH) for their technical assistance.

References


