"Biological rhythms, higher brain function, and behavior: gaps, opportunities and challenges"

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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 these diseases. 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) gaps and challenges to advancing knowledge on the link between disrupted circadian rhythms/sleep and psychiatric disorders, and (4) 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. The review is organized around five themes pertinent to: (1) the impact of molecular clocks on physiology and behavior, (2) interactions between circadian

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signals and cognitive functions, (3) the interface of circadian rhythms with sleep (4) a clinical perspective on the relationship between circadian rhythm abnormalities and affective disorders, and (5) pre-clinical models of circadian rhythm abnormalities and mood disorders.

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 hours, and can be synchronized with the external temporal environment by light and nonphotic 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 (Seretti et al., 2003; Benedetti et al., 2005), SAD (Johansson et al., 2003), and autism spectrum disorders (Nicholas et al., 2007; 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-HT_{1A}, 5-HT_2, or 5-HT_7 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 (Royball et al., 2007). Alterations in neuroeptide 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., 2001). 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 identifies 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 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) 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) 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

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, SAD, as well as mood, anxiety, and substance use disorders (Benca, 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., 2005). 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 oscillators 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 GSK3β, 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). Norpineine 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 (*sss*), 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 glucogen 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 (Dudley 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.

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 on 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; Deurveilher 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; Deurveilher 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 rhyhtmicity 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 Abreau, 2006; Levitan, 2007), 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 a (Goldman and Nelson, 1993). Melatonin not only mediates seasonal changes, but also affects influences circadian rhythms and sleep [see (Dubocovich, 2007), for review]. 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., 2005; 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 Swaab, 2006) and (Duncan, 2007)]. Reports that selective serotonin dennervation 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-HT_{1B} 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- HT_7 receptors in the hamster DRN, strongly attenuating circadian phase shifts induced by microinjection of serotonergic agonists in this region (Duncan et al., 1999; Duncan et al., 2004). The age-related loss of 5-HT_7 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 psychopathophysiological 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.

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 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 (Tononi and Cirelli, 2003). 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; Riedner 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/circadian rhythms 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 on-going 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 suggest 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 $5HT_{1A}$ 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 neuropil 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 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 (*Zonotricia 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, Pfister-Genskow, et al., 2008; Jones, Vyazovskiy, et al., 2008, 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 adolescents, 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.

Circadian Rhythm Abnormalities and Affective Disorders-Clinical Perspective

Data on the influence of clock genes and circadian rhythm abnormalities on psychopathology and treatment response is 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., 2005; 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., 2003). 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., 2003; Benedetti et al, 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; Frank et al., 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 preclinical 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.

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, ethylnitrosourea (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)* knock-out 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* knock-out 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* knock-outs 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 $1\varepsilon/\delta$ 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 CK1 ε/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 rhyhtmicity 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 bio-markers 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.

Abbreviations

CLOCK	circadian locomoter output cycles kaput
Npas2	neuronal PAS domain protein 2
Per1, Per2	period homologue 1 and 2
Cry1, Cry2	cryptochrome 1and 2
GSK3β	Glycogen synthase kinase 3 beta
PGC-1alpha	peroxisome proliferator-activated receptor gamma coactivator-1 alpha
SPECT	single photon emission computed tomography
VIP	vasoactive intestinal peptide

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References

Adli M, Hollinde DL, Stamm T, Wiethoff K, Tsahuridu M, Kirchheiner J. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta −50T/C single nucleotide polymorphism. Biol Psych 2007;62:1295–1302.

Allison KC, Ahima RS, O'Reardon JP, Dinges DF, Sharma V, Cummings DE. Neuroendocrine profiles associated with energy intake, sleep, and stress in the night eating syndrome. J Clin Endocrinol Metab 2005;90:6214–6217. [PubMed: 16131578]

Aston-Jones G, Bloom FE. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J Neurosci 1981;1:876–886. [PubMed: 7346592]

Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. Nature Neurosci 2001;4:732–738. [PubMed: 11426230]

Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005;28:403–450. [PubMed: 16022602]

Badura L, Swanson T, Adamowicz W, Adams J, Cianfrogna J, Fisher K, Holland J, Kleiman R, Nelson F, Reynolds L, St Germain K, Schaeffer E, Tate B, Sprouse J. An inhibitor of casein kinase I epsilon induces phase delays in circadian rhythms under free-running and entrained conditions. J Pharmacol Exp Ther 2007;322:730–738. [PubMed: 17502429]

Barbini B, Benedetti F, Colombo C, Dotoli D, Bernasconi A, Cigala-Fulgosi M. Dark therapy for mania: a pilot study. Bipolar Disorders 2005;7:98–101. [PubMed: 15654938]

Beaulieu JM, Zhang X, Rodriguiz RM, Sotnikova TD, Cools MJ, Wetsel WC. Role of GSK3 beta in behavioral abnormalities induced by serotonin deficiency. Proc Natl Acad Sci USA 2008;105:1333–1338. [PubMed: 18212115]

Benca RM. Sleep in psychiatric disorders. Neurologic Clinics 1996;14:739–764. [PubMed: 8923493]

Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspezia S, Pontiggia A. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: acute response and long-term remission rates. J Clin Psych 2005;66:1535–1540.

Benedetti F, Colombo C, Sorretti A, Lorenzi C, Pontiggia A, Barbini B. Antidepressant effects of light therapy combined with sleep deprivation are influenced by a functional polymorphism within the promoter of the serotonin transporter gene. Biol Psych 2003;54:687–692.

Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene *Per3* influences age at onset of bipolar disorder. Neurosci Lett 2008;445:184–187. [PubMed: 18789374]

Benedetti F, Sorretti A, Colombo C, Barbini B, Lorenzi C, Campori E. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. Am J Med Genetics B (Neuropsych Genetics) 2003;123:23–26.

Benedetti F, Sorretti A, Colombo C, Campori E, Barbini B, di Bella D. Influence of a functional polymorphism within the promoter of the serotonin transporter gene on the effects of total sleep deprivation in bipolar depression. Am J Psych 1999;156:1450–1452.

Benedetti F, Sorretti A, Pontiggia A, Bernasconi A, Lorenzi C, Colombo C. Long-term response to lithium salts in bipolar illness is influenced by the glycogen synthase kinase 3-beta −50 T/C SNP. Neurosci Lett 2005;376:51–55. [PubMed: 15694273]

Birketvedt GS, Florholmen J, Sundsfjord J, Osterud B, Dinges D, Bilker W. Behavioral and neuroendocrine characteristics of the night-eating syndrome. J Am Med Assoc 1999;282:657–663.

Borbely AA, Acherman P. Sleep homeostasis and models of sleep regulation. J Biol Rhyth 1999;14:557–568.

Bourgeron, T. The possible interplay of synaptic and clock genes in autism spectrum disorders; Cold Spring Harbor Symposium on Quantum Biology; 2007. p. 645-654.Review

Blumberg MS, Seelke AMH, Lowen SB, Karlsson KAE. Dynamics of sleep-wake cyclicity in developing rats. Proc Natl Acad Sci USA 2005;102:14860–14864. [PubMed: 16192355]

Carskadon MA, Acebo C, Jenni OG. Regulation of adolescent sleep: implications for behavior. Ann NY Acad Sci 2004;1021:276–291. [PubMed: 15251897]

Chaudhury D, Loh DH, Dragich JM, Hagopian A, Colwell CS. Select cognitive deficits in vasoactive intestinal peptide deficient mice. BMC Neurosci 2008;9:63–75. [PubMed: 18616823]

Chaudhury D, Colwell CS. Circadian modulation of learning and memory in fear-conditioned mice. Behav Brain Res 2002;133:95–108. [PubMed: 12048177]

Chaudhury D, Wang LM, Colwell CS. Circadian regulation of hippocampal long-term potentiation. J Biol Rhythms 2005;20:225–236. [PubMed: 15851529]

Chaudhury D, Loh DH, Dragich JM, Hagopian A, Colwell CS. Select cognitive deficits in vasoactive intestinal peptide deficient mice. BMC Neurosci 2008;9:63–75. [PubMed: 18616823]

Chen R, Seo DO, Bell E, von Gall C, Lee C. Strong resetting of the mammalian clock by constant light followed by constant darkness. J Neurosci 2008;28:11839–11847. [PubMed: 19005049]

Cirelli C, Gutierrez CM, Tononi G. Extensive and divergent effects of sleep and wakefulness on brain gene expression. Neuron 2004;41:35–43. [PubMed: 14715133]

Colombo C, Lucca A, Benedetti F, Barbini B, Campori E, Smeraldi E. Total sleep deprivation combined with lithium and light therapy in the treatment of bipolar depression: replication of main effects and interaction. Psych Res 2000;95:43–53.

Colten, HR.; Altevogt, BM. Institute of Medicine's Committee on Sleep Medicine and Research. Washington, DC: The National Academies Press; 2006. Sleep disorders and sleep deprivation: An unmet public health problem; p. 404

Crocker A, Sehgal A. Octopamine regulates sleep in *Drosophila* through protein kinase A-dependent mechanisms. J Neurosci 2008;28:9377–9385. [PubMed: 18799671]

Deurveilher S, Semba K. Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: Implications for the circadian control of behavioural state. Neurosci 2005;130:165–183.

Dudley CA, Erbel-Sieler C, Estill SJ, Reick M, Franken P, Pitts S, McKnight SL. Altered patterns of sleep and behavioral adaptability in *NPAS2*-deficient mice. Science 2003;301:379–383. [PubMed: 12843397]

Duman RS. Synaptic plasticity and mood disorders. Mol Psych 2002;7:S29–S34.

Duncan MJ. Aging of the mammalian circadian timing system: Changes in the central pacemaker and its regulation by photic and nonphotic signals. Neuroembryol Aging 2007;4:85–101.

Duncan MJ, Crafton CJ, Wheeler DL. Aging regulates 5-HT$_{1B}$ receptors and serotonin reuptake sites in the suprachiasmatic nucleus and other brain regions. Brain Res 2000;856:213–219. [PubMed: 10677628]

Duncan MJ, Grear KE, Hoskins MA. Aging and SB-269970-A, a selective 5-HT$_7$ receptor antagonist, attenuate circadian phase advances induced by microinjections of serotonergic drugs in the hamster dorsal raphe nucleus. Brain Res 2004;1008:40–48. [PubMed: 15081380]

Duncan MJ, Hensler JG. Aging alters in a region-specific manner serotonin transporter sites and 5-HT1A receptor-G protein interactions in hamster brain. Neuropharmacol 2002;43:36–44.

Duncan MJ, Short J, Wheeler DL. Comparison of the effects of aging on 5-HT$_7$ and 5-HT$_{1A}$ receptors in discrete regions of the circadian timing system in hamsters. Brain Res 1999;829:39–45. [PubMed: 10350528]

Dubocovich ML. Melatonin receptors: Role on sleep and circadian rhythm regulation. Sleep Medicine 2007;8:34–42. [PubMed: 18032103]

Ehlen JC, Grossman GH, Glass JD. In vivo resetting ot the hamster circadian clock by 5-HT7 receptors in the suprachiasmatic nucleus. J Neurosci 2001;21:5351–5357. [PubMed: 11438611]

Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. Sleep 2007;30:1617–1630. [PubMed: 18246972]

Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, et al. Reduced sleep spindle activity in schizophrenia patients. Am J Psych 2007;164:483–492.

Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagiolini AM. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. Archiv Gen Psych 2005;62:996–1004.

Frank E, Soreca I, Swartz HA, Fagiolini AM, Mallinger AG, Thase ME. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. Am J Psychiatry 2008;165:1559–1565. [PubMed: 18829872]

Fredriksen K, Rhodes J, Reddy R, Way N. Sleepless in Chicago: tracking the effects of adolescent sleep loss during the middle school years. Child Devel 2004;75(1):84–95. [PubMed: 15015676]

Gall AJ, Todd WD, Ray B, Coleman CM, Blumberg MS. The development of day-night differences in sleep and wakefulness in norway rats and the effect of bilateral enucleation. J Biol Rhythms 2008;23:232–241. [PubMed: 18487415]

Gannon RL, Millan MJ. Serotonin$_{1A}$ autoreceptor activation by S 15535 enhances circadian activity rhythms in hamsters: Evaluation of potential interactions with serotonin$_{2A}$ and serotonin$_{2C}$ receptors. Neurosci 2006;137:287–299.

Garcia JA, Zhang D, Estill SJ, Michoff C, Rutter J, Reick M, Scott K, Diaz-Arrastia R, McKnight S. Impaired cued and contextual memory in *NPAS2* deficient mice. Science 2000;288(5474):2226–2230. [PubMed: 10864874]

Geda YE, Knopman DS, Mrazek DA, Jicha GA, Smith GE, Negash S, Boeve BF, Ivnik RJ, Petersen RC, Pankratz VS, Rocca WA. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment: A prospective cohort study. Arch Neurol 2006;63:435–440. [PubMed: 16533972]

Goldman, BD.; Nelson, RJ. Melatonin and seasonality in mammals. In: Yu, H-S.; Reiter, RJ., editors. Melatonin: Biosynthesis, physiological effects, and clinical applications. Boca Raton: CRC Press; 1993. p. 225-252.

Gompf HS, Aston-Jones G. Role of orexin input in the diurnal rhythm of locus coeruleus impulse activity. Brain Res 2008;1224:43–52. [PubMed: 18614159]

Gonzalez MM, Aston-Jones G. Circadian regulation of arousal: role of the noradrenergic locus coeruleus system and light exposure. Sleep 2006;29:1327–1336. [PubMed: 17068987]

Gonzalez MMC, Aston-Jones G. Light deprivation damages monoamine neurons and produces a depressive behavioral phenotype in rats. Proc Natl Acad Sci USA 2008;105:4898–4903. [PubMed: 18347342]

Hakkarainen R, Johansson C, Kieseppä T, Partonen T, Koskenvuo M, Kaprio J, Lonnquivst J. Seasonal changes, sleep length and circadian preference among twins with bipolar disorder. BMC Psychiatry 2003;3:6. [PubMed: 12795811]

Hampp G, Ripperger JA, Houben T, Schmutz I, Blex C, Perreau-Lenz S, Brunk I, Spanagel R, Ahnert-Hilger G, Meijer JH, Albrecht U. Regulation of monoamine oxidase A by circadian-clock components implies clock influences on mood. Current Biology 2008;18:678–683. [PubMed: 18439826]

Handa RJ, Zoeller RT, McGivern RF. Changes in vasoactive intestinal peptide and arginine vasopressin expression in the suprachiasmatic nucleus of the rat brain following foot shock stress. Neurosci Lett 2007;2:99–104. [PubMed: 17826907]

Harvey AG, Mullin BC, Hinshaw SP. Sleep and circadian rhythms in children and adolescents with bipolar disorder. Dev Psychopathol 2006;18(4):1147–1168. [PubMed: 17064432]

Hofman MA, Swaad DF. Living by the clock: the circadian pacemaker in older people. Ageing Research Reviews 2006;1:33–51. [PubMed: 16126012]

Horvath TL, Peyron C, Diano S, Ivanov A, Kilduff TS, van den Pol AN. Hypocretin (orexinn) activation and synaptic innervation of the locus coeruleus noradrenergic system. J Comp Neurol 1999;415:145–159. [PubMed: 10545156]

Huber R, Ghilardi MF, Massimini M, Ferrarelli F, Riedner BA, Peterson MJ. Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. Nature Neurosci 2006;9:1169–1176. [PubMed: 16936722]

Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. Nature 2004;430(6995):78–81. [PubMed: 15184907]

Hummer DL, Jechura TJ, Mahoney MM, Lee TM. Gonadal hormone effects on entrained and free-running circadian activity rhythms in the developing diurnal rodent Octodon degus. Am J Physiol Regul Integr Comp Physiol 2007;292:586–597.

Hunsley MS, Palmiter RD. Altered sleep latency and arousal regulation in mice lacking norepinephrine. Pharmacol Biochem Behav 2004;78:765–773. [PubMed: 15301933]

Ikeda M, Yoshioka T, Allen CN. Developmental and circadian changes in Ca2+ mobilization mediated by GABAA and NMDA receptors in the suprachiasmatic nucleus. Eur J Neurosci 2003;17:58–70. [PubMed: 12534969]

Jenni OG, Achermann P, Carskadon MA. Homeostatic sleep regulation in adolescents. Sleep 2005;28:1446–1454. [PubMed: 16335485]

Jenni OG, Carskadon MA. Spectral analysis of the sleep electroencephalogram during adolescence. Sleep 2004;27:774–783. [PubMed: 15283014]

Jones S, Pfister-Genskow M, Benca RM, Cirelli C. Molecular correlates of sleep and wakefulness in the brain of the white-crowned sparrow. J Neurochem 2008;105:46–62. [PubMed: 18028333]

Jones SG, Vyazovskiy VV, Cirelli C, Tononi G, Benca RM. Homeostatic regulation of sleep in the white-crowned sparrow (Zonotrichia leucophrys gambelii). BMC Neurosci 2008;9:47. [PubMed: 18505569]

Jorm AF. Is depression a risk factor for dementia or cognitive decline? Gerontol 2000;46:219–227.

Karl T, Burne TH, Herzog H. Effects of Y1 receptor deficiency on motor activation, exploration and anxiety. Behav Brain Res 2006;167:87–93. [PubMed: 16203045]

King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, Steeves TD, Vitaterna MH, Kornhauser JM, Lowrey PL, Turek FW, Takahashi JS. Positional cloning of the mouse circadian clock gene. Cell 1997;89:641–653. [PubMed: 9160755]

Koh K, Joiner WJ, Wu MN, Yue Z, Smith CJ, Sehgal A. Identification of SLEEPLESS, a sleep-promoting factor. Science 2008;321:372–376. [PubMed: 18635795]

Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metab 2007;6:414–421. [PubMed: 17983587]

Kumar R, Parslow RA, Jorm AF, Rosenman SJ, Maller J, Meslin C, Anstey KJ, Christensen H, Sachdev PS. Clinical and neuroimaging correlates of mild cognitive impairment in a middle-aged community sample: the personality and total health through life 60+ study. Dementia and Geriatric Cognitive Disorders 2006;21:44–50. [PubMed: 16254430]

Lamont EW, Legault-Coutu D, Cermakian N, Boivin DB. The role of circadian clock genes in mental disorders. Dialog Clin Neurosci 2007;9:33–42.

Laposky AD, Bass J, Kohsaka A, Turek FW. Sleep and circadian rhythms: key components in the regulation of energy metabolism. FEBS Lett 2008;582:142–151. [PubMed: 17707819]

Lewy AJ, Lefler BJ, Emens JS, Bauer VK. The circadian basis of winter depression. Proc Natl Acad Sci USA 2006;103:7414–7419. [PubMed: 16648247]

Liu X. Sleep and adolescent suicidal behavior. Sleep 2004;7:1351–1358. [PubMed: 15586788]

Liu C, Li S, Liu T, Borjigin J, Lin JD. Transcriptional coactivator PGC-1α integrates the mammalian clock and energy metabolism. Nature 2007;447:477–481. [PubMed: 17476214]

Lo CC, Chou T, Penzel T, Scammell TE, Strecker RE, Stanley HE, Ivanov PCH. Proc Natl Acad Sci USA 2004;101(14):17545–17548. [PubMed: 15583127]

Lundgren JD, Newberg AB, Allison KC, Wintering NA, Ploessl K, Stunkard AJ. 123I ADAM SPECT imaging of serotonin transporter binding in patients with night eating syndrome: a preliminary report. Psych Res 2008;162:214–220.

Mansour HA, Wood J, Logue T, Chowdari KV, Dayal M, Kupfer DJ, Monk TH, Devlin B, Nimgaonkar VL. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. Genes Brain Behav 2006;5:150–157. [PubMed: 16507006]

McClung CA. Circadian genes, rhythms and the biology of mood disorders. Pharmacol Ther 2007;114:222–232. [PubMed: 17395264]

McClung CA, Sidiropoulou K, Vitaterna M, Takahashi JS, White FJ, Cooper DC, Nestler EJ. Regulation of dopaminergic transmission and cocaine reward by the Clock gene. Proc Natl Acad Sci USA 2005;102:9377–9381. [PubMed: 15967985]

Meyer-Bernstein EL, Morin LP. Destruction of serotonergic neurons in the median raphe nucleus blocks circadian rhythm phase shifts to triazolam but not to novel wheel access. J Biol Rhythms 1998;13:494–505. [PubMed: 9850010]

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Kogan JN, Sachs GS. Intensive psychosocial intervention enhances functioning in patients with bipolar depression: results from a 9-month randomized controlled trial. Am J Psych 2007;164:1340–1347.

Miyaoka T, Yasukawa R, Tsubouchi K, Miura S, Shimizu Y, Sukegawa T. Successful treatment of nocturnal eating/drinking syndrome with selective serotonin reuptake inhibitors. Int J Clin Psychopharmacol 2003;18:175–177.

Moore RY, Eichler VB. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. Brain Res 1972;42:201–206. [PubMed: 5047187]

Morera AL, Abreu P. Seasonality of psychopathology and circannual melatonin rhythms. J. Pineal Research 2006;3:279–283. [PubMed: 16948790]

Naylor E, Bergmann BM, Krauski K, Zee PC, Takahashi JS, Vitaterna MH, Turek FW. The circadian clock mutation alters sleep homeostasis in the mouse. J Neurosci 2000;20:8138–8143. [PubMed: 11050136]

Novati A, Roman V, Cetin T, Hagewoud R, den Boer JA, Luiten PGM. Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. Sleep 2008;31:1579–1585. [PubMed: 19014078]

O'Reardon JP, Peshek A, Allison KC. Night eating syndrome : diagnosis, epidemiology and management. CNS Drugs 2005;19:997–1008. [PubMed: 16332142]

O'Reardon JP, Ringel BL, Dinges DF, Allison KC, Rogers NL, Martino NS. Circadian eating and sleeping patterns in the night eating syndrome. Obesity Res 2004;12:1789–1796.

Owens JA. Sleep disorders and attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 2008;10(5):439–444. [PubMed: 18803919]

Payne JL, Quiroz JA, Zarate CA, Manji HK. Timing is everything: does the robust upregulation of noradrenergically regulated plasticity genes underlie the rapid antidepressant effects of sleep deprivation? Biol Psych 2002;52:921–926.

Prendergast BJ, Nelson RJ. Affective responses to changes in day length in Siberian hamsters (*Phodopus sungorus*). Psychoneuroendocrinol 2005;30:438–452.

Pyter LM, Reader BF, Nelson RJ. Short photoperiods impair spatial learning and alter hippocampal dendritic morphology in adult male white-footed mice (*Peromyscus leucopus*). J Neurosci 2008;25:4521–4526. [PubMed: 15872099]

Roeder T. Tyramine and octopamine: Ruling behavior and metabolism. Ann Rev Entomol 2005;50:447–477. [PubMed: 15355245]

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. Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci USA 2007;104:6406–6411. [PubMed: 17379666]

Rattenborg NC, Mandt BH, Obermeyer WH, Winsauer PJ, Huber R, Wikelski M. Migratory sleeplessness in the white-crowned sparrow (Zonotrichia leucophrys gambelii). PLoS Biology 2004;2:212.

Ruby NF, Hwang CE, Wessells C, Fenrandez F, Zhang P, Sapolsky R, Heller HC. Hippocampal-dependent learning requires a functional circadian system. Proc Natl Acad Sci USA 2008;105:15593–15598. [PubMed: 18832172]

Seelke AMH, Blumberg MS. The microstructure of active and quiet sleep as cortical delta activity emerges in infant rats. Sleep 2008;31:691–699. [PubMed: 18517038]

Shaltiel G, Maeng S, Malkesman O, Pearson B, Schloesser RJ, Tragon T, Rogawski M, Gasior M, Luckenbaugh D, Chen G, Manji HK. Evidence for the involvement of the kainate receptor subunit GluR6 (GRIK2) in mediating behavioral displays related tobehavioral symptoms of mania. Mol Psychiatry 2008;13:858–872. [PubMed: 18332879]

Shearman LP, Weaver DR. Distinct pharmacological mechanisms leading to c-fos gene expression in the fetal suprachiasmatic nucleus. J Biol Rhythms 2001;16(6):531–540. [PubMed: 11760011]

Shin K, Schaffer A, Levitt AJ, Boyle MH. Seasonality in a community sample of bipolar, unipolar and control subjects. J Affect Dis 2005;86:19–25. [PubMed: 15820267]

Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activities are eliminated by hypothalamic lesions. Proc Natl Acad Sci USA 1972;69:1583–1586. [PubMed: 4556464]

Stunkard AJ, Grace WJ, Wolff HG. The night-eating syndrome; a pattern of food intake among certain obese patients. Am J Med 1955;19:78–86. [PubMed: 14388031]

Stunkard AJ, Allison KC, Lundgren JD, Martino NS, Heo M, Etemad B, O' Reardin JP. A paradigm for facilitating pharmacotherapy at a distance: sertraline treatment of the night eating syndrome. J Clin Psychiatry 2006;67:1568–1572. [PubMed: 17107248]

Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order anddisorder: implications for physiology and disease. Nature Rev Genetics 2008;10:764–775. [PubMed: 18802415]

Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: Efficacy, protocol, safety, and side effects. CNS Spectr 2005;10:647–663. [PubMed: 16041296]

Tominaga K, Shibata S, Ueki S, Watanabe S. Effects of 5-HT$_{1A}$ receptor agonist on the circadian rhythm of wheel running activity in hamsters. Eur J Pharmacol 1992;214:79–84. [PubMed: 1316283]

Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. Brain Res Bull 2003;62:143–150. [PubMed: 14638388]

Murphy M, Riedner BA, Huber R, Massimini M, Ferrarelli F, Tononi G. Source modeling sleep waves. Proc Natl Acad Sci USA 2009;106:1608–1613. [PubMed: 19164756]

Tu BP, Kudlicki A, Rowicka M, McKnight SL. Logic of the yeast metabolic cycle: Temporal compartmentalization of cellular processes. Science 2003;310:1152–1158. [PubMed: 16254148]

Tu BP, McKnight SL. Metabolic cycles as an underlying basis of biological oscillations. Nature Rev Mol Cell Biol 2006;7:696–701. [PubMed: 16823381]

Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. Science 1999;283:549–554. [PubMed: 9915705]

Viola AU, Archer SN, James LM, Groeger JA, Lo JCY, Skene DJ. PER3 polymorphism predicts sleep structure and waking performance. Current Biol 2007;17:613–618.

Vyazovskiy VV, Cirelli C, Pfister-Genskow M, Faraguna U, Tononi G. Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. Nature Neurosci 2008;11:200–208. [PubMed: 18204445]

Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G. Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. Sleep 2007;30:1631–1642. [PubMed: 18246973]

Wehr TA, Duncan WC, Sher L, Aeschbach D, Schwartz PJ, Turner EH. A circadian signal of change of season in patients with seasonal affective disorder. Archiv Gen Psych 2001;58:1108–1114.

Welsh S, Yoo A, Liu J, Takahashi JS, Kay S. Bioluminescence imaging of individual fibroblasts reveals persistent, independently phased circadian rhythms of clock gene expression. Current Biol 2004;14:2289–2295.

Workman JL, Weil ZM, Tuthill CR, Nelson RJ. Maternal pinealectomy increases depressive-like responses in Siberian hamster offspring. Behav Brain Res 2008;189:387–391. [PubMed: 18328579]

Wu JC, Kelsoe JR, Schachat C, Bunney BG, DeModena A, Golshan S, Gillin JC, Potkin SG, Bunney WE. Rapid and sustained antidepressant response with sleep seprivation and chronotherapy in bipolar disorder. Biological Psychiatry. 2009 0006-3223/09.

Yang S, Van Dongen HPA, Wang K, Berrettini W, Bućan M. Assessment of circadian function in fibroblasts of patients with bipolar disorder. Mol Psychiatry 2008;14:143–155. [PubMed: 18301395]

Yoo S, Hu PT, Gujar N, Jolesz FA, Walker MP. A deficit in the ability to form new human memories without sleep. Nature Neurosci 2007;10:385–392. [PubMed: 17293859]