

The sleep–circadian interface: A window into mental disorders

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Sleep, circadian rhythms, and mental health are reciprocally interlinked. Disruption to the quality, continuity, and timing of sleep can precipitate or exacerbate psychiatric symptoms in susceptible individuals, while treatments that target sleep–circadian disturbances can alleviate psychopathology. Conversely, psychiatric symptoms can reciprocally exacerbate poor sleep and disrupt clock-controlled processes. Despite progress in elucidating underlying mechanisms, a cohesive approach that integrates the dynamic interactions between psychiatric disorder with both sleep and circadian processes is lacking. This review synthesizes recent evidence for sleep–circadian dysfunction as a transdiagnostic contributor to a range of psychiatric disorders, with an emphasis on biological mechanisms. We highlight observations from adolescent and young adults, who are at greatest risk of developing mental disorders, and for whom early detection and intervention promise the greatest benefit. In particular, we aim to a) integrate sleep and circadian factors implicated in the pathophysiology and treatment of mood, anxiety, and psychosis spectrum disorders, with a transdiagnostic perspective; b) highlight the need to reframe existing knowledge and adopt an integrated approach which recognizes the interaction between sleep and circadian factors; and c) identify important gaps and opportunities for further research.

mental disorder | mood disorder | psychosis | sleep | chronobiology

Mood, anxiety, and psychotic disorders rank among the most prevalent contributors to the burden of disability and disease worldwide (1), yet our understanding of their causes, and targets for therapeutic intervention, remains limited. In this perspective, we argue that a closer integration of psychiatry with sleep and circadian science will catalyze the improved understanding and treatment of mental disorders.

Sleep–circadian disturbances are the rule, rather than the exception, across every diagnostic category of psychiatric disorder (2). In addition to being a risk factor for the subsequent development of psychopathology (3), problems with sleep and its timing are one of the earliest signs of relapse (4). Challenges to the sleep–circadian system through nightshift work increases the risk of developing depression and anxiety disorder (5) while 8% of individuals with depression experience deterioration in mood over winter (6), implicating shortened day-length and changes in light exposure in mood disorders. Carefully controlled laboratory studies have elucidated that sleep homeostatic and circadian processes contribute to diurnal mood variation in healthy volunteers (7), and these processes may contribute to the observations from field-based studies that mood symptoms, including anxiety and risk of suicide, are greater in the mornings (Fig. 1).

Intervention studies have begun to reveal how targeting sleep–circadian disturbances can also lead to improvements in comorbid psychiatric symptoms (13). Most such interventions are

yet to enter widespread clinical practice, however, and when presenting together with psychiatric disorder, sleep problems are often overlooked. How do we harness the potential of sleep and chronobiology to foster innovation and improve the lives of those living with mental illness?

We address this critical question by integrating clinical and translational sleep–circadian findings in mood, anxiety, and psychosis spectrum disorders over the past two decades, and set out a roadmap of key barriers, gaps, and facilitators to progress. Foremost, although the interaction between circadian rhythmicity and sleep homeostasis has been well characterized in the classical two-process model of sleep regulation (14), studies in psychiatric disorders have largely examined sleep and circadian function as independent and parallel processes. We illustrate how both are implicated in a range of psychiatric disorders, and adopting a transdiagnostic approach that integrates the dynamic interaction between sleep and circadian processes with behavioral and environmental

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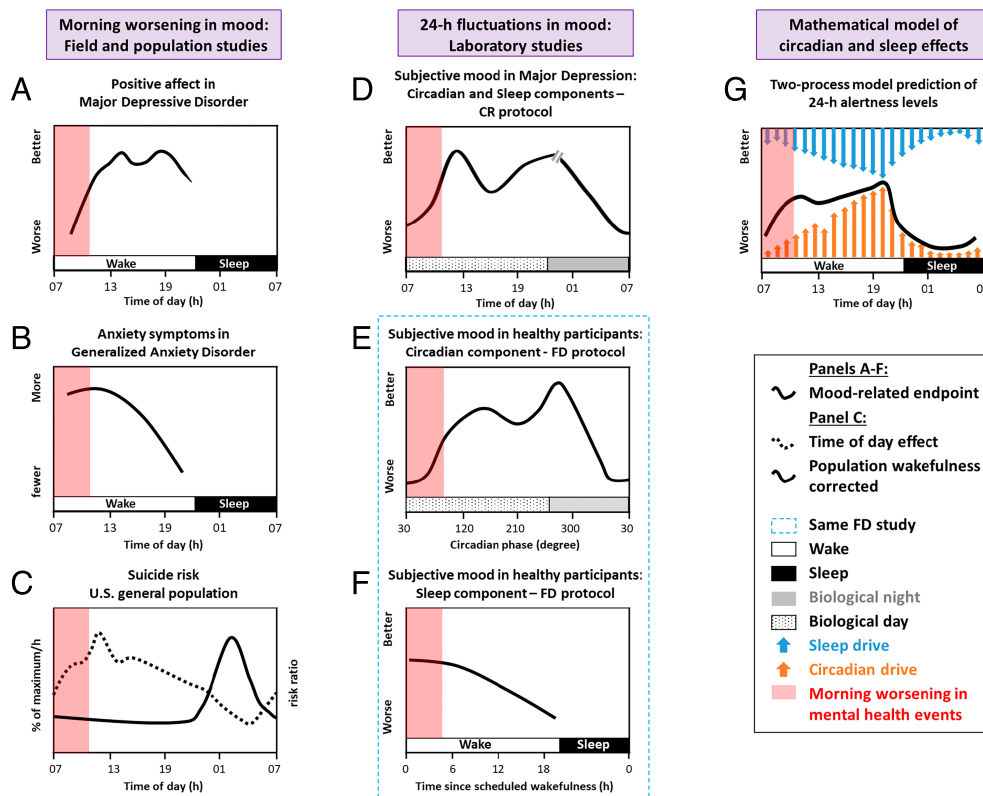


Fig. 1. Contribution of sleep and circadian factors to diurnal mood variation and greater probability of adverse psychiatric outcomes during the morning hours. Field studies in patient populations demonstrate (A) lower mood (8), (B) greater anxiety symptoms (9), and (C) elevated suicide risk, after adjusting for population sleep/wake timing (solid line) and greater proportion of suicides per hour (dotted line) (10) in the morning, indicating a diurnal rhythm in these variables when sampled under real-world conditions. Note that these time courses are likely to be underpinned by multiple additional factors (e.g., alcohol use and social isolation may contribute to elevated suicide risk) and show significant individual differences. Measures of outcomes such as suicide differ depending on the type of study and assumptions of the analysis. Stringently controlled laboratory protocols allow the contribution of sleep homeostasis and circadian factors on mood to be disentangled from environmental and behavioral influences. (D) Constant routine (CR) study illustrating the modulation of mood by sleep homeostatic and circadian processes across the 24-h cycle, in women with depression (11). (E and F) Forced desynchrony (FD) protocol revealing the relative contribution of the endogenous circadian and sleep homeostatic process on mood in healthy control participants (12). These are representative, and not definitive, time-courses. (G) the two-

process model posits that sleep and alertness are regulated by the close interaction of two counterpoised processes—homeostatic sleep pressure and the circadian system. Although alertness, (black line) and not mood, is predicted by the mathematical model, note that the time-course for alertness is similar to that for the circadian component of mood in the forced desynchrony study.

variables, promises to deliver a richer understanding of the mechanisms underpinning mental disorder, and in turn promote the development of blended interventions that address them. Sleep and circadian physiology evolve over the lifespan to play essential, age-specific roles in neuroplasticity and brain maturation (15). We therefore pay particular attention to adolescence—a time over which sleep–circadian disturbance is likely to play critical roles in the development of psychiatric disorders.

Transdiagnostic Associations Between Sleep–Circadian Disturbance and Mental Disorder

The notion that common sleep–circadian profiles are seen across mental disorders is compelling, as it suggests not only that shared sleep–circadian mechanisms play a role in the development and maintenance of psychiatric symptoms, but also that the same sleep–circadian interventions might be effective in treating both sleep–circadian and psychiatric symptoms, across a range of disorders (16).

The elevated prevalence of sleep disorders across mood, anxiety, and psychotic disorders, summarized in *SI Appendix, Table S1* supports a transdiagnostic formulation. Insomnia occurs more commonly in mental disorders than in the general population (17), both during remission, and even more so during acute mood episodes (18) or in early psychosis (19, 20), when difficulty falling and staying asleep affects over half of individuals. Although data are limited in anxiety-related and bipolar disorders, nightmares are also significantly more common across psychiatric disorders, and associated with greater symptom severity and elevated risk of suicidality (21). Studies investigating circadian rhythm sleep–wake disorders (CRSWD) are scarce; however, those that are available

suggest sleep-timing disorders, particularly delayed sleep–wake phase disorder, are present in 32% of bipolar (22) and 8% of early psychosis (20) patients. Another important yet under-recognized transdiagnostic phenotype is hypersomnia, characterized by an increased quantity of, or excessive need for, sleep (≥ 10 h of sleep needed during 24-h). In bipolar disorder, hypersomnia predicts relapse of mood episodes (23). Notably, hypersomnia co-exists with insomnia in around a quarter (18) to a third (24) of individuals with mood disorder, and similar proportions in psychosis (20, 25), suggesting that as well as experiencing disturbed sleep initiation and maintenance at night, patients are more sleepy during the day, spend longer in bed and/or have a longer overall sleep duration, in a vicious cycle. Indeed, co-morbidity within individuals is the norm (26): Of 121 adults receiving treatment in a community mental health center, over 85% met full or subdiagnostic criteria for two or more sleep–circadian problems (13). Similarly high rates of co-morbidity have been reported in psychosis (20), with both insomnia and nightmare disorder occurring together in 33% of patients.

Do objective measures support a transdiagnostic approach? Case-control actigraphy has been the most widely employed objective measure, permitting meta-analyses in depression (27), bipolar disorder (28, 29), early psychosis (30), and schizophrenia (29, 31). Here, data show notable consistency across diagnostic categories: parameters consistent with insomnia (reduced total sleep time, increased sleep latency and sleep fragmentation), hypersomnia (greater time in bed, reduced daytime activity), CRSWD (delayed sleep–wake timing), together with increased variability in sleep timing between days, have been reported across depression, euthymic and depressed phases of bipolar disorder, anxiety disorder, and psychosis (*SI Appendix, Table S1*). Similar patterns have been found in at-risk and early bipolar disorder (32), but findings were less consistent in at-risk and early psychosis (30).

A strength of actigraphy is that it allows the concurrent and longitudinal investigation of both sleep and wake dimensions, and the relative timing of each phase, under free-living conditions. In inter-episode bipolar disorder, patients show reduced daytime activity with shorter duration of the active phase, lower amplitude rest-activity rhythms, and also less organized and predictable patterns of motor behavior (33, 34), with the latter being identified as a heritable phenotype (34). In a study combining actigraphy with mobile symptom monitoring, unidirectional associations between motor activity and depressed mood, and bidirectional associations between motor activity and sleep, were found (35), suggesting that activation is a distinct dimension of bipolar disorder that is intimately connected with sleep and psychopathology. Other studies have reported unique motor signatures in schizophrenia and depression, using nonlinear analysis (36). The effects of antipsychotic medication on activation in schizophrenia, however, may be a significant confounding variable. These findings advocate for further research which examines the inter-relationships between activation, sleep, and symptomatology and integrates them with concepts of hypersomnia.

Findings from circadian and polysomnography studies have been less consistent, due in part to heterogeneous patient groups, medication effects, methodological limitations such as masking, as well as notable areas where evidence is lacking (see *SI Appendix* for a summary of sleep-circadian principles, definitions, and measures). Circadian markers have been studied in mood disorder (37), discussed below; however, in anxiety and psychosis-spectrum disorders (38), findings are sparse and conflicting, making it difficult to reach firm conclusions. Of the meta-analyses of polysomnographic studies, indices of poorer sleep continuity and shorter sleep time have been reported in depression, anxiety disorders, and early and chronic stages of psychosis (2, 19, 39, 40), and increased REM pressure were found in depression, obsessive compulsive disorder (OCD), and chronic psychosis (2, 39). Within the anxiety-related disorders, reduction in sleep time and increased rapid eye movement (REM) pressure were particularly pronounced in OCD (40), suggesting a differential profile to the other anxiety disorders. In comparison to actigraphy, few significant differences in polysomnographic parameters were found in inter-episode bipolar disorder. In the following sections, we examine some of the putative mechanisms by which these perturbations may interact to play a causal role in the development and maintenance of psychiatric symptoms.

Mechanisms Underlying Sleep-Circadian Disturbance in Psychiatric Disorders

Longitudinal Sleep-Circadian Interactions and the Development of Mental Disorders. Adolescence and early adulthood are a time of elevated risk of onset of mood, psychotic, and substance use disorders (41), with a recent US Task Force recommending screening for depression in adolescents aged 12 to 18 (42). This critical window coincides with widespread changes in the structure and timing of sleep and provides a prototypical example of the dynamic and inseparable interplay between sleep and circadian processes and their association with mental health.

During adolescence, developmental shifts in sleep physiology, including slow wave dynamics, sleep spindles, and sleep need, index maturational changes in gray and white matter (43, 44). These changes are accompanied by concurrent shifts in sleep timing, underpinned by the slower accumulation of homeostatic sleep pressure, and delay in the phase of the endogenous circadian rhythm (45). These variables interact with environmental and behavioral factors including exposure to evening light and greater autonomy in deciding bedtimes, thereby promoting a longer phase relationship between circadian timing and bedtime, pushing bedtimes even later (46). Later sleep onset, however, is

often incompatible with social schedules including school start times, leading to curtailed sleep duration and the accumulation of sleep debt during school days. Adolescents may compensate for sleep debt by sleeping longer and later on free days, resulting in greater variability in the duration and timing of sleep over the week (47) and misalignment between circadian and sleep-wake rhythms so-called "social jet-lag" (48). In turn, the risk of sleep disturbances, and adverse health and mental health outcomes, are increased (47).

Interindividual variations in sleep-circadian physiology appear to confer vulnerability to developing psychiatric disorders. A preference for later bedtimes and rise times (late chronotype) and/or excessively delayed sleep timing during adolescence have been associated with a range of disorders, including depression (49), anxiety (50), bipolar disorders (51), psychosis (52), and suicidality (53). Conversely, Mendelian randomization approaches indicate that genes associated with an earlier, "morningness" chronotype are associated with a lower risk of developing depression, supporting a causal link between chronotype and mood disorder (54). A greater magnitude of sleep and social rhythm disturbance has been observed in young people with depressive or bipolar disorders compared with healthy controls (55), and a higher prevalence of delayed sleep phase syndrome has been found in the depressed phase of bipolar disorder, compared with unipolar depression (56). Similar associations have been reported in the few studies utilizing objective measures of sleep timing and circadian phase (57). Lower relative amplitude and more irregular diurnal rest-activity rhythms were observed in young people with emerging mood disorders, with less robust rhythms also being associated with greater symptom severity (58).

Though defined phenotypically, late chronotype is determined by a number of endogenous sleep-circadian variables, including a longer circadian period leading to a later phase of entrainment (59), lower light sensitivity (60), and differences in sleep-homeostasis dynamics. Together, these vulnerabilities may interact with age-dependent changes in physiology, environmental and social variables, to place some young people at increased risk of developing sleep-circadian disorder, and a range of psychiatric disorders (43).

Genetic Associations. Our understanding of the molecular mechanisms linking sleep-circadian factors with psychiatric disorders is founded on animal studies focusing on the contribution of clock genes (Fig. 2). Targeted disruption of molecular or cellular rhythms in the mouse suprachiasmatic nucleus (SCN) increases depression and anxiety-related behaviors, suggesting that clock machinery contributes to the regulation of mood, anxiety, and reward (64, 65). Manipulation of core circadian genes within mood and reward-related circuits can also lead to changes in neuronal activity and behavior, though the results are more complex. For example, knock-down of *Per1* and *Per2* specifically in the mouse nucleus accumbens (NAc), a central hub for emotion and reward regulation, leads to increased anxiety-related behavior (66) while a knock-down of the *Clock* paralogue *Npas2* in the NAc leads to decreased anxiety-related behavior (67).

In humans, although associations between polymorphisms in circadian genes including *CLOCK*, *PER*, *TIMELESS*, and *RORA* have been implicated in mood disorders (37, 68), the genetic landscape for sleep-circadian interactions with psychiatric disorders has more recently built upon studies of heritability in rest-activity phenotypes using large-scale accelerometer and genome-wide association study (GWAS) datasets. These approaches have identified numerous independent genetic loci associated with chronotype/sleep timing (34, 69) and sleep quality/duration (70), including insomnia (71). Polygenic risk score for low relative amplitude in rest-activity profiles from UK Biobank participants was significantly associated with depression and also mood instability and neuroticism (72).

Both candidate-gene and GWAS approaches have yet to reveal consistent and robust associations between clock genes and

psychiatric disorder (37, 68). However, recent human data implicate associations between a combination of variants in many genes and a range of heritable trait-like sleep–circadian endophenotypes, including later sleep timing, longer sleep duration, sleep fragmentation, and lower amplitude of rest–activity rhythm, that are not unique to any one disorder. These traits associate with phenotypes such as mood instability, neuroticism, and paranoia, thereby playing a role in the pathophysiology of psychiatric disorders. Novel analysis pipelines using state-of-the-art algorithms for classifying accelerometer data (73) promise to further extend the utility of such large-scale datasets, by identifying more nuanced digital biomarkers of sleep–circadian phenotypes.

Light. Substantial evidence implicates the duration, timing, and intensity exposure to light with mental illness. Much of this interest has centered on mood disorder, following from the observation that depression can emerge or worsen over autumn and winter months, correlating with shortening of photoperiod (6), and that light therapy has antidepressant effects in seasonal, unipolar, and bipolar depression (74, 75). A recent analysis of a population-level survey, for example, found that greater self-reported time outdoors was associated with lower cross-sectional and longitudinal probability of mood disorder (76). Light in anxiety and psychotic disorders have received far less attention, an exception being a recent study reporting an association between greater variability in sleep timing in schizophrenia with reduced duration of exposure to bright light (77).

Mis-timed and low-amplitude light exposure can drive misalignment and diminished amplitude of the endogenous pacemaker through the pathway from the nonimage forming ipRGCs to the SCN, and in turn affect pathways downstream from the SCN (Fig. 2), including the sleep-promoting VLPO, other hypothalamic areas involved in appetite and homeostasis, and nuclei involved in mood regulation such as the dorsal raphe (78). Additionally, the SCN has dense serotonergic innervation, and one mechanism by which selective serotonin reuptake inhibitor antidepressants may exert therapeutic effects is by amplifying the nonvisual effects of light (79) and phase-advancing circadian rhythms (80). A 50-fold interindividual difference in sensitivity of the circadian system to light (81), arising from age, sex, ocular and genetic factors, and photic history (60), may explain why certain individuals are more susceptible to developing circadian dysfunction, and mood disorder, in response to aberrant light input.

Beyond its effects on the clock, however, understanding has more recently extended to include the effects of light on sleep, alertness, cognitive function, and mood, through pathways that are independent of the SCN and visual systems (78, 82). Light modulates sleep homeostasis and slow-wave sleep (83), possibly through a melanopsin-dependent direct pathway from ipRGCs to the VLPO (78). Evidence from rodent models suggests that light also affects alertness via direct pathways from the ipRGCs to monoaminergic and orexinergic centers and the VLPO, and mood via projections to the amygdala, nucleus accumbens, and perihabenular nucleus (82, 84). Serotonin, dopamine, and norepinephrine levels and activity of neurons expressing these neurotransmitters are also strongly influenced by photoperiod length (85), and positive correlations between serotonin synthesis and hours of sunlight have been reported (86).

Light is a particularly powerful explanatory variable because it provides a mechanistic and testable link between the behavioral and environmental context and sleep–circadian biology. Environmental factors in the home can lead to low quantity and quality of daylight (87), while symptoms such as low mood and motivation, anhedonia, negative symptoms, and paranoia may predispose to behaviors that reduce exposure to daylight, and increase exposure to light at night. Together, these factors may result in an attenuated

amplitude and aberrant timing of the light signal. Thus far, these contextual factors have received little systematic investigation in mental disorders, however. Integrating these levels of explanation with a more detailed measurement of light exposure across psychiatric diagnoses, and their effects on both circadian and noncircadian pathways, is a key goal.

Circadian Misalignment. “Circadian health” has been defined as the condition in which circadian clocks are allowed to stably entrain to zeitgebers, and thereby establish and appropriate, stable phase relationship in its cyclic environment (88). Displacement in timing between the central circadian pacemaker and daily environmental and behavioral rhythms, including the light–dark and sleep–wake cycles, is therefore hypothesized to negatively impact mood and well-being, and contributes to the increased risk of mood disorders among night workers (5) and psychiatric disorders more widely (Fig. 2). It was first postulated that the timing of the central circadian clock in depression is abnormally early relative to the timing of the sleep/wake cycle, such that a “critical phase” of the circadian rhythm that is normally aligned with wakefulness, is advanced into sleep (89, 90). More recent clinical studies have pointed toward delayed circadian phase relative to sleep (91, 92), with severity of misalignment correlating with the severity of depressive symptoms both in patients with depression (91) and seasonal affective disorder (SAD) (93).

In bipolar disorder, sleep–wake cycle abnormalities can precede mood fluctuations (94), with shortened, fragmented, and irregularly timed sleep during manic or depressive episodes. A ~7 h phase advance in cortisol rhythm and *PER1* and *ARNTL1* (also known as *BMAL1*) expression has been reported in mania, and 4 to 5 h phase delay in the depressed phase (95). Misalignment subsequently normalized upon successful treatment of mood. Consistent with the hypothesis that circadian misalignment plays a causal role in mood disorder, the use of lithium—a mood stabilizer used primarily in the treatment and prophylaxis of mania—appears to have a direct effect on the molecular clock, perhaps through phosphorylation and inhibition of *GSK3 β* , resulting in a lengthening of cellular and behavioral period, with consequent phase delay and slowing of the clock (96). In schizophrenia, abnormalities in the circadian organization of sleep–wake cycles have been less well characterized, though delayed and advanced sleep phases, free running rest–activity patterns, or irregular sleep–wake patterns have been reported (97), which also predict clinical deterioration (98).

Given the far-reaching effects of circadian timing on the structure of sleep, circadian misalignment may exert some of its pathophysiological effects by virtue of its effects on sleep. Few clinical studies, however, have concurrently investigated sleep, using polysomnography or actigraphy, together with circadian parameters, and this area warrants greater attention.

Recent developments suggest a connection between the microbiome and mental health. Circadian misalignment may increase inflammatory microbiota taxa and decrease microbiota-tryptophan biosynthesis (99), and disrupted microbiome profile is associated with increased systemic inflammation and symptom severity in major depression (61, 100). Hence, sleep–circadian factors regulating the microbiome are a putative mechanism in the onset and maintenance of psychiatric disorders (Fig. 2).

Neuroplasticity. A fundamental function of sleep is hypothesized to be the consolidation and active reorganization of information that has accrued during wakefulness through long-term synaptic potentiation (LTP) (101). The synaptic homeostasis hypothesis (102) is a candidate mechanism by which the efficiency and signal-to-noise ratio of neuronal networks are maintained within a dynamic working range, through selective down-scaling of synaptic strength during slow-wave sleep (Fig. 2). For example, the amount of slow-

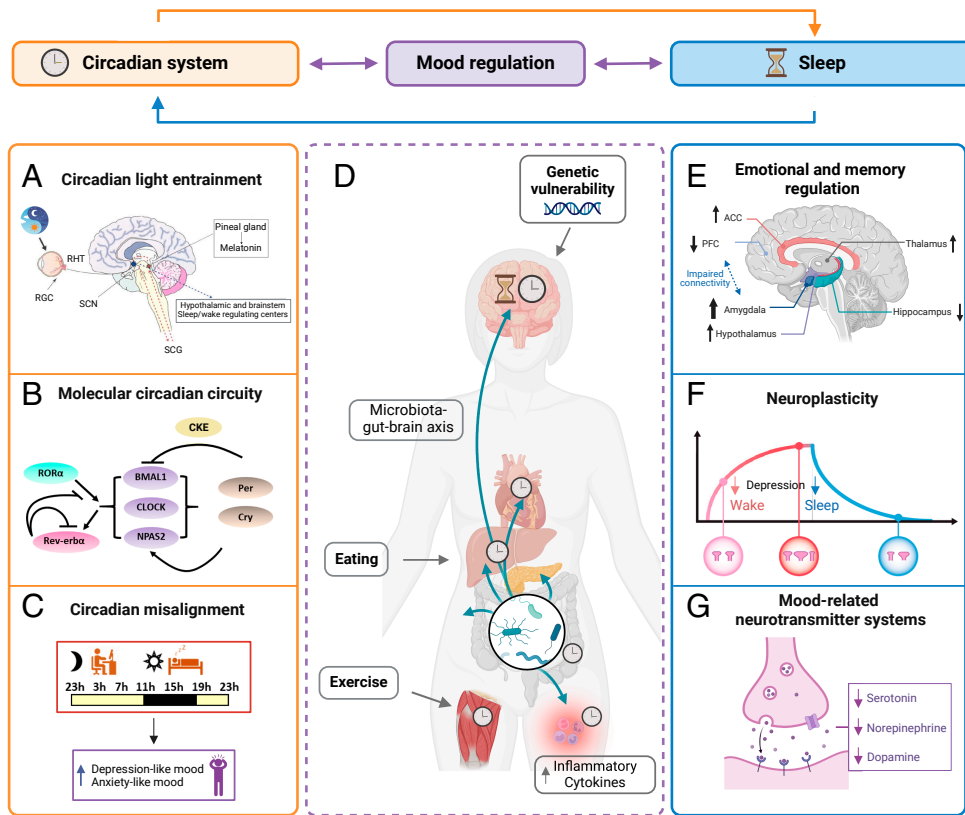


Fig. 2. Conceptual framework of circadian (Left) and sleep (Right) mechanisms in mental disorders. (A) Nonvisual light information is conveyed from the retina to areas involved in arousal, emotion, and cognition through an indirect pathway via the SCN, but also through direct pathways which bypass the SCN. Mistimed or low-amplitude light exposure can therefore exert widespread effects on sleep, alertness, and mood. (B) Circadian rhythmicity is generated by the transcription of core clock genes and their suppression by their protein products. (C) Misalignment between the endogenous circadian timing system and behavioral or environmental cycles can negatively affect mood. (D) Physical activity and eating that occurs at a nonoptimal circadian phase, leading to misalignment between central and peripheral clocks, have been implicated in the pathogenesis of mood disorder. Preliminary findings in healthy humans also suggest that alterations in the gut microbiome influence mood via circadian mechanisms (5, 61) and increase depression and anxiety-like symptoms in healthy participants (62). (E–G) Sleep disturbances, particularly insomnia, are implicated in mood dysregulation through several pathways including maladaptive emotional processing, aberrant neuroplasticity and memory consolidation, and dysregulated neurotransmitter signaling (63). For instance, depression reduces both increase in synaptic density build up during wakefulness and increase synaptic pruning during sleep (black arrow, F). We

emphasize, however, the many points of interaction and synergy between sleep and circadian systems. Abbreviations: RHT, retino hypothalamic tract; RGC, retinal ganglion cells; SCN, suprachiasmatic nucleus; SCG, superior cervical ganglion; ACC, anterior cingulate cortex; PFC, prefrontal cortex.

wave activity during sleep reflects net synaptic strength, and underlying slow oscillations may contribute directly to synaptic renormalization (102).

In depression, diminished LTP-like plasticity, and deficient accumulation and dissipation of homeostatic sleep pressure (103), have been demonstrated in preclinical and human studies (104). There is indirect human evidence in support of deficient LTP in depression: Using the paired associative stimulation paradigm, significantly lower motor evoked potentials were found in depression relative to controls, with patients who responded to sleep deprivation showing higher inducibility of associative LTP-like plasticity than nonresponders (104). In this context, it is notable that total and partial (first or second half of the sleep episode) sleep deprivation paradigms have shown comparable efficacy in the treatment of unipolar and bipolar depression, with one meta-analysis reporting a significant response in 50 to 60% of patients (105). The synaptic homeostasis hypothesis has been invoked to account for the efficacy of sleep deprivation, by boosting net synaptic strength and shifting the inducibility of associative plasticity into an optimal window, thereby reversing LTP impairments associated with depression (104, 106). Nonetheless, although response to sleep deprivation is rapid, benefits are not sustained, with deterioration of mood following recovery sleep occurring in 80% of patients. Wake therapy has therefore yet to be widely adopted in clinical practice, and prolonging its therapeutic effects remains an important challenge.

Circadian timing influences every aspect of physiology, including neuroplasticity. The initial encoding of experiences during the active phase, and their consolidation into hippocampal and cortical structures, are both energetically demanding processes which are hypothesized to be apportioned by clock-controlled processes into wakefulness and sleep, respectively (107). Centrally mediated mechanisms including 24-h rhythms of corticosteroid

and melatonin secretion, fluctuations in brain temperature, and GABAergic inhibition together provide the appropriate conditions for circadian-dependent modulation of plasticity (107). The implications of sleep that is mistimed with respect to circadian phase on aberrant neuroplasticity underlying psychiatric disorders, however, has yet to be explored.

Insomnia, Cognition and Emotional Regulation. Insomnia is a prevalent sleep disorder that is likely to play an important causal role in the development and maintenance of most psychiatric disorders, with which it is highly co-morbid (3, 108). Characterized by hyperarousal with consequent difficulty in falling and staying asleep, the increased vulnerability to depression and anxiety in insomnia has been hypothesized to arise from instability in REM sleep and impaired overnight emotional memory regulation, which in turn impedes adaptation to emotional distress (63). This results in greater hyperarousal and associated stress reactivity, rumination, and cognitive impairments during wakefulness, which interact with sleep and circadian physiology, and in turn amplifies these vulnerabilities in a bidirectional feedback loop (Fig. 2).

More broadly, animal studies also indicate that sleep is essential for the offline processing and encoding of episodic and emotional memory in limbic, striatal, and neocortical regions (109). These experiments have informed a model of how neural signatures of waking experience are reactivated during ensuing sleep, prioritizing consolidation of salient information into long-term memory (110). Disruption to these mechanisms may therefore contribute to inaccurate and unstable mental models of the world, the misassociation of different aspects of experience, and impairments in setting that experience in its correct emotional context (111). Animal models (112) and electroencephalography (EEG) or magnetoencephalography (MEG) studies in adults with schizophrenia (113)

have demonstrated reduced sleep spindle density and dyscoordination of spindles and slow-waves across the cortex, potentially reflecting dysfunctional (cortico-)thalamo-cortical synchrony downstream of synaptic abnormalities in underlying circuits (19, 114).

However, the extent to which these EEG abnormalities coincide with symptoms such as insomnia or circadian misalignment remains unclear, since most patient EEG studies are relatively small and run over one or two nights in sleep laboratory settings. Setting studies of sleep-dependent information processing in circadian context—for example by quantifying memory consolidation relative to different circadian phases—remains a fundamental and clinically relevant next step. In addition, the term insomnia is often used imprecisely, as a symptom rather than as a diagnosis, and in some cases, the sleep disturbance may be more accurately explained by intermixed disorders including circadian rhythm sleep-wake disorder, nightmares, and night terrors, all of which are over-represented in mental disorders (20, 21).

Sleep and Circadian Interventions in Psychiatric Disorders

Targeting the diverse sleep and circadian risk factors and disease mechanisms discussed above, particularly over critical neurodevelopmental windows, offers an opportunity for developing novel preventative and therapeutic interventions for psychiatric disorders. These range from population-level considerations, such as the timing of the school and work day and the design of the built environment which optimizes light exposure from a sleep-circadian perspective; to personalized interventions including psychological therapies, neuromodulation, and medication and meal timing that are tailored to individual circadian parameters (*SI Appendix, Fig. S1*).

Cognitive Behavioral Therapy for Insomnia (CBT-I). CBT-I is a multimodal psychological therapy that addresses cognitive factors and behaviors that perpetuate insomnia (115). International guidelines endorse CBT-I as first-line treatment (116) and meta-analysis of randomized trials finds improvement in both night and daytime symptoms (117, 118).

While investigation of treatment mechanisms is in its infancy, mediation analyses within randomized trials suggest CBT-I works, at least in part, through reduction of dysfunctional beliefs about sleep and cognitive arousal (119). To improve mechanistic precision, more recent work has systematically interrogated individual components of CBT-I, like sleep restriction therapy, showing reduced pre-sleep arousal, increased sleep consolidation, and potentiated EEG delta power and decreased beta power during NREM sleep (120, 121). CBT-I may also improve the regularity of the sleep-wake pattern and realign circadian phase angle, by delaying sleep opportunity (122).

Anxiety and depressive symptoms have been assessed as secondary outcomes in trials of CBT-I, and have been shown to reduce after treatment, relative to waiting-list or psychological placebo controls (118). Reductions in insomnia were also found to mediate depression improvement (123). A smaller number of trials have assessed the effect of CBT-I on symptoms of psychiatric disorders in specific patient groups. For example, a recent meta-analysis (108) found that CBT-I reduced depressive symptoms in patients with depression, and reduced trauma symptoms in patients with post-traumatic stress disorder (PTSD). However, the number of trials and sample sizes have been small to date, and there is uncertainty around whether treatment effects are maintained at follow-up. Another approach has been to treat insomnia in the absence of comorbidity and assess whether treatment leads to reduced incidence of future psychiatric disorder. A recent trial found that CBT-I reduced both the incidence and recurrence of major depression in elderly adults compared to control (124).

In contrast to depression, there has been limited evaluation of CBT-I in the context of anxiety disorders and psychosis. Intriguingly, in a head-to-head comparison of digital CBT-I versus digital cognitive behavioral therapy (CBT) for generalized anxiety, both treatments improved anxiety symptoms, yet CBT-I had larger initial effects on insomnia (125). There is also a need to examine the brain and behavioral mechanisms through which CBT-I leads to improvement in psychopathology, and to test whether combining sleep and circadian treatments (126), or personalizing sleep treatment based on presenting sleep and circadian phenotype (127) can enhance mental health outcomes.

Noninvasive Brain Stimulation. Sleep is a highly active process, characterized by reactivation and reorganization of waking experience (110). Given the hypothesized contribution of dysfunctional nocturnal replay and neuroplasticity to psychiatric disorders, the use of noninvasive brain stimulation to selectively enhance or disrupt specific sleep stages, particularly slow-wave sleep, and impede maladaptive processing, has attracted interest.

Transcranial magnetic stimulation (TMS) employs magnetic pulses designed to induce action potentials in localized cortical areas, whereas the transcranial electrical stimulation (tES) paradigm uses weak electric currents to drive local shifts in neuronal excitability, that extends across the neural network (128). Auditory stimulation (AS) during sleep may activate arousal, or induce brief global reductions in cortical excitability, depending on the strength of stimulus (129). Phase-locking tES and AS to up- or down-phases of slow wave sleep has been shown to strengthen or suppress slow-oscillations and evoke K-complexes, while extended trains of stimulation can gradually entrain the frequency of neuronal activity to that of the stimulus (128).

The effects of slow wave modulation using noninvasive brain stimulation on sleep physiology and memory consolidation have been studied in healthy adults (128). With the exception of TMS, however, these approaches are currently experimental, and studies that examine its potential in treating psychiatric disorders remain scarce. In the context of theories of deficient neuroplasticity in depression (106, 130), selective attenuation of slow waves using tES or AS may function as a more acceptable alternative compared with sleep deprivation. Signatures seen in other disorders, such as deficient sleep spindles in schizophrenia (131), may also be targeted by tES, which has been shown to augment spindle activity and procedural memory in healthy adults (132). Finally, brain stimulation has received little attention in REM sleep, and modulating REM sleep may be particularly relevant in light of theories of REM instability and aberrant emotional processing in insomnia, depression, anxiety, and PTSD (63).

Light Therapy. With wide-ranging effects on sleep and circadian biology, emotion, and cognition through on both circadian and noncircadian pathways, light is one of the most studied nonpharmacological, biologically oriented treatment approaches in psychiatry. Therapeutic use of light arose from the hypothesis that seasonal depression results from a shortened photoperiod and lack of daylight over winter months, with most consistent effects of morning bright light therapy having been demonstrated in SAD (93). Efficacy of light therapy against placebo has subsequently been demonstrated in unipolar (74) and bipolar depression (75). Superiority of combination light therapy plus medication over pharmacotherapy alone has also been reported, and in unipolar depression, equivalent effect sizes to treatment with SSRIs (133). Recent findings suggest light is effective in treating perinatal depression (134); however, robust studies in psychosis and anxiety disorders are lacking (135). Combined light therapy with sleep deprivation and sleep phase-shifting may be more effective and durable than light therapy alone (136).

Light therapy is typically delivered on rising in the morning, which targets the phase advance portion of the phase–response curve, while also encouraging regular rise times (137). Bright light may also have antidepressant effects by directly modulating monoaminergic pathways that regulate mood (82), increasing alertness, and strengthening homeostatic sleep pressure (133). Appropriately timed light therapy also results in modest improvements in sleep timing and continuity in neuropsychiatric disorders (135); the extent to which improvements in sleep–circadian parameters mediate the effects on psychopathology is an important and as yet unexplored avenue of investigation.

Though recommended as a first-line treatment option of moderate to severe depression (75), the optimal parameters including the timing, duration, and intensity of dose, light spectra, and duration of treatment remain unclear, and larger and longer trials are needed. Consensus guidelines suggest the overall risk of switches in mood polarity from depression to mania in bipolar disorder is low (75); however, close monitoring and pre-treatment with a mood stabilizer are nonetheless recommended.

Chronopharmacology. The administration of medications can be timed with respect to circadian phase, in order to optimize efficacy, minimize adverse effects, or modulate circadian rhythms. For example, when taken in the morning, the antipsychotic drug aripiprazole resulted in significantly favorable lipid and cholesterol measures compared to evening dosing (138), while evening dosing of risperidone was associated with greater weight gain and elevated glycosylated hemoglobin when compared to morning dosing (139). Melatonin taken in the evening promotes phase-advance of the circadian clock in delayed sleep–wake phase disorder and may have beneficial effects on psychopathology in other disorders where comorbid sleep–circadian disturbance is suspected (140).

Certain medications used in the treatment of mood disorders have direct effects on the molecular clock which may underlie their therapeutic efficacy (141). Lithium lengthens the period of the clock and increases amplitude of the rhythm *in vitro* (142). Importantly, studies using patient-derived fibroblast (143) and neuronal precursor cells (144) found that cells with a longer period and lower amplitude have a weak circadian response to lithium, and these patients are more likely to be lithium nonresponders (145). In contrast, cells taken from lithium responders tended to have a short circadian period and be more responsive to the circadian effects of lithium (144, 145). SSRI antidepressants have also been shown to cause large phase advances in SCN neuronal activity (80) and increase the melatonin-suppressing effects of light (79). Thus, SSRIs and morning bright light therapy may modulate the circadian clock through a common circadian mechanism. There are also indications that rapid-acting antidepressants such as ketamine, which is acutely wake-promoting, change circadian gene expression, similar to total sleep restriction, and changes to sleep–wake profiles in response to ketamine can predict the durability of antidepressant effect (146).

Timed Meals and Exercise. Although nutrition and exercise have long been associated with mental health (147), whether the timing of food intake or exercise influences mental health is a recent question. In humans, food timing can influence peripheral circadian rhythms, without impacting circadian rhythms driven by the central circadian clock (148). Conversely, timed exercise can shift the central circadian clock, including under dim-light conditions (149), but there are no human data testing whether physical activity can shift peripheral clocks. The circadian timing of meals and exercise have also been shown to differentially influence physiological functions, including glucose control, energy expenditure, and cardiovascular risk (150).

In shift-workers, a recent randomized controlled trial showed that while simulated night work with night eating increased

depression-like and anxiety-like impairments, daytime eating prevented mood impairment during simulated night work (62). These beneficial effects of daytime eating correlated with the degree of synchrony between central and peripheral circadian rhythms, suggesting that meal timing is a promising countermeasure against the adverse mental health effects of night work. Regarding timed exercise in psychiatric disorders, future carefully controlled clinical trials are needed.

Conclusions and Future Directions

A central objective for the field is to develop treatment approaches that target sleep–circadian disturbances, and also address concomitant psychiatric symptoms, by virtue of the two sharing overlapping mechanisms. Though incomplete, current evidence suggests that there are many commonalities in subjective and objectively determined sleep–circadian profiles between psychiatric diagnoses, in the prodromal, early, and established phases of disorder. What is not yet clear is how common patterns of sleep–circadian dysfunction are differentially expressed and contribute to unique psychiatric phenotypes. Are the pathways through which circadian misalignment, insomnia, or sleep deprivation drive mania in bipolar disorder similar to those that might lead to the emergence of delusions and hallucinations in nonaffective psychosis? Although there is mounting evidence for overlapping genetic, cellular, and neurotransmitter mechanisms that underlie both sleep–circadian and mood symptoms in depression and bipolar disorder (151), similar links are lacking in psychosis-spectrum disorders, particularly from the circadian perspective. A further important area of future work will be to understand interindividual vulnerability with respect to sleep–circadian disturbance: Why are some individuals susceptible to developing mental disorder in the face sleep–circadian disruption, while others not?

Addressing these questions demands an integrated, coordinated research agenda (*SI Appendix, Box 2*). We advocate future studies which concurrently examine sleep and circadian parameters across multiple conditions and symptom clusters, in order to identify areas of diagnostic specificity, and convergence. Much research to date has been fragmented by its focus on specific age groups, and longitudinal approaches which capture changes across the lifespan are necessary. Promoting the adoption of common, operationalized standards for the collection of biomarkers of sleep, activity, and circadian rhythms (152–154) will aid harmonization across research groups.

A related question is how sleep–circadian disruption interacts with environmental and behavioral factors on the causal pathway to psychiatric disorder. Laboratory studies have afforded valuable insights into the role of homeostatic sleep and circadian processes in sleep–wake regulation (14, 155). They are limited however in their integration of variables such as light, social schedules, and psychopathology under real-world conditions and overlook the complex and dynamic interplay between vulnerabilities in sleep and circadian function, developmental trajectory, behavior and environment, and psychiatric disorder. Devices have been developed which allow investigation of the nonvisual effects of light, at the ocular level (156). Remote sleep-sensing technologies including wireless EEG, wearable sleep trackers, and mobile devices (157) may aid measurement of sleep, rest-activity patterns, and light exposure across developmental time-points in the home setting and reveal critical windows of vulnerability in which to focus preventative interventions. Together with improvements in automated sleep scoring algorithms, these technologies may facilitate real-time sleep analysis and closed-loop neurostimulation paradigms that recursively adapt to the effects of modulation on sleep physiology (128).

Studies examining circadian biomarkers in mental illness are scarce, even though accurate assessment of circadian phase is

essential in understanding the contribution of circadian misalignment to psychopathology and for informing the correct timing of light or melatonin therapy. For example, up to 20% of individuals with a diagnosis of insomnia initiate sleep at too early a circadian phase (158), suggesting a circadian contribution to the disorder in a subset of individuals. Experimental approaches including multivariate-based biomarkers from blood samples (159), and the combination of physiologically informed mathematical models (45) with data from rest-activity profiles from wearable accelerometers (160), show promise in estimating circadian phase at scale, at least in those with fixed sleep schedules, and will help to uncover the contribution of circadian dysfunction to disease.

A further goal is to promote cost-effective and scalable interventions that are effective across different categories of psychiatric disorder. With the exception of CBT-I, and in more specialist settings melatonin and light therapy, pharmacological and behavioral sleep-circadian therapies are yet to enter widespread clinical practice. Aided by a closer theoretical and practical convergence of chronobiology with sleep science, the development of technologies which allow longitudinal measurement of sleep and circadian variables in the field, improved education in sleep medicine among clinicians and rigorous clinical trials, a key opportunity exists for overcoming barriers to clinical translation.

Current sleep and chronotherapeutic interventions are mostly supported by evidence from uncontrolled within-subject designs, or small randomized controlled trials which test a single intervention against the current standard of care or placebo. We have argued however that the contribution of sleep and circadian disturbances to psychopathology is multifactorial; examining each component in isolation can be inefficient and fails to account for the complexity of sleep-circadian problems experienced by people living with psychiatric disorder (26). Innovative multi-component interventions such as the Transdiagnostic Intervention for Sleep and Circadian dysfunction (26) adopt a sleep-health framework to combine modules that address sleep and circadian dimensions including sleep regularity, sleep phase, daytime dysfunction, nightmares, excessive

time in bed, and the sleep environment, that are applicable to a range of disorders including depression, bipolar disorder, and psychosis. Such approaches acknowledge the co-morbidity of sleep-circadian pathology in psychiatric disorders, but also their associations with a spectrum of psychiatric phenotypes. Similar composite interventions could be tested and refined through efficient multarm, multistage adaptive trial designs, and adherence to treatments such as sleep restriction can potentially be enhanced by leveraging wearable and smartphone technologies. Future work should also untangle the complex mechanisms by which reduced activity and social behavior, psychotropic medications, and co-morbidities including nightmares, parasomnias, and sleep-disordered breathing, all of which are over-represented in mental disorder, contribute both directly and indirectly to psychopathology and disability via sleep and circadian pathways.

Collectively, research into mental health is poised to take advantage of the extraordinary advances that have been made in sleep and circadian science and translate these into improved understanding of the pathophysiology and treatment of psychiatric disorders.

Data, Materials, and Software Availability. There are no data underlying this work.

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