PNAS

Supporting Information for

The sleep-circadian interface: a window into mental disorders

N. Meyer, R. Lok, C. Schmidt, S. D. Kyle, C. McClung, C. Cajochen, F.A.J.L. Scheer, M.W. Jones, S.L. Chellappa

Corresponding authors: Nicholas Meyer/ Sarah Chellappa.
E-mail: nicholas.meyer@kcl.ac.uk; S.L.Chellappa@soton.ac.uk

This PDF file includes:

Supporting text
Fig. S1
Table S1
SI References

Supporting Information Text

Sleep and circadian rhythms: principles, interactions and definitions

The sleep and circadian systems are two distinct but continually interacting and coordinated processes, which in health give rise to a stable level of alertness during the day, and consolidated periods of sleep that are aligned with the night, and regularly timed across days of the week (1).

Arousal is generated by brainstem, hypothalamic and basal forebrain nuclei, which activate the thalamus and cortex through ascending monoamine, acetylcholine, histamine, and glutamate pathways (2). Wakefulness is modulated by orexin signalling, and accompanied by the accumulation of sleep-promoting somnogens, including adenosine (3), which signals the homeostatic need for sleep. In response to adenosine, and also signals from the circadian system, sleep is initiated by the GABA-ergic inhibition of the wake-promoting centres by the ventrolateral preoptic area (VLPO) and the median preoptic nucleus (MnPO) in the rostral hypothalamus (2). Medications including antipsychotic and certain antidepressant agents cause sedation by blocking serotonin, noradrenaline, dopamine and histamine receptors, while the widely prescribed selective-serotonin reuptake inhibitors (SSRIs) promote arousal by potentiating serotonin signalling. Electroencephalogram (EEG) measurement of brain activity is the principal biomarker of sleep, with an adult typically first entering deep NREM sleep, and then cycling between NREM and REM sleep every 90 minutes.

How is sustained daytime alertness maintained in the face of mounting sleep pressure, and regularity in the timing of sleep and wakefulness, orchestrated? Through its indirect projections to sleep and wake-promoting centres, via the hypothalamus, the central circadian pacemaker in the suprachiasmatic nucleus (SCN) delivers an increasing wake-promoting signal throughout the waking day, which counterbalances the mounting homeostatic sleep signal. Near the time of habitual sleep-onset, the circadian wake-promoting signal rapidly dissipates, accompanied by melatonin release and falling body temperature, and sleep ensues (4). Rhythmicity in the SCN, as well as nearly every cell in the brain and body, are controlled by the transcription and translation of core clock genes in interlocking, autoregulatory feedback loops, with a period of approximately 24 hours (5). Importantly, the timing of the endogenous circadian rhythm is synchronised with environmental cycles through the process of entrainment, thereby preventing the former from drifting out of alignment with the latter. In humans, the light-dark cycle is the primary signal of entrainment, acting through non-image forming intrinsically photosensitive retinal ganglion cells (ipRGCs); evening light exposure delays the circadian clock, while morning light advances the clock (6). A glossary of sleep-circadian terms, including circadian dysfunction, is provided in the supplement.

In addition to regulating when sleep occurs within the 24-hour day, sleep propensity, duration, and structure are all under circadian influence. Laboratory studies indicate that sleep latency is shortest when sleep onset coincides with the lowest point of the circadian alerting signal, while sleep duration and efficiency are greatest when the midpoint of sleep is centred on the circadian nadir, soon after which the propensity for REM sleep is also greatest (7). Sleep spindles (7), slow wave sleep (8), as well as vigilance and cognition during wakefulness (9), are also modulated by circadian phase.

Conversely, sleep and waking behaviours influence circadian timing (10). Closing of the eyelids reduces light intensity at the retina, thereby modulating circadian phase and amplitude, while exposure to light in the evening, or keeping the curtains closed in the morning, exert a delay in phase of the circadian pacemaker. SCN neuronal firing also varies with sleep stage, with high activity during REM sleep, and low activity during NREM sleep (11), though the relevance of this finding to the circadian control of sleep remains uncertain.

Biomarkers of the endogenous circadian rhythm include salivary, urinary and plasma melatonin, cortisol and core body temperature rhythms (4). Distinguishing circadian markers from commonly reported measures of diurnal rhythms such as sleep-wake behaviours (typically measured using actigraphy) is critical, as the two are often conflated. Although a picture of delayed sleep-wake timing may suggest a delay in phase of the underlying circadian rhythm, sleep timing, as discussed above, is the product of the interaction between sleep homeostasis and the circadian system. Establishing the circadian contribution to a given sleep-wake phenotype is only possible, therefore, by sampling biomarkers of circadian phase, and the ability to elucidate underlying mechanisms using diurnal measures alone is otherwise significantly limited. Furthermore, interpretation of endogenous circadian markers may be complicated by *masking*, in which environmental factors obscure endogenous circadian markers, for example by light exposure suppressing melatonin secretion. These factors therefore need to be controlled for, particularly in real-world settings. Another methodological challenge involves delineating whether circadian disturbance arises in a state or trait manner. For example, a stable, trait-like delay in dim-light melatonin onset is more likely to indicate a primary circadian disturbance, whereas an acute, state-like delay in melatonin timing may occur secondary to psychological and behavioural factors, such as the emergence of a mood episode resulting in insomnia and exposure to evening light. Longitudinal and concurrent measurement of environmental and contextual influences, including light and the sleeping environment, is necessary in disentangling these variables.

Box 1: Glossary of sleep and circadian terms

- ***Actigraphy***: measurement of the rest-activity profile using a wearable accelerometer, typically placed on the non-dominant wrist, from which sleep and activity parameters can be estimated.
- ***Chronotherapeutics***: a treatment or intervention which modulates the endogenous circadian rhythm, or the use of an intervention with respect to the timing of the endogenous circadian rhythm, with the objective of

maximizing efficacy and minimizing toxicity and adverse effects.

- ***Chronotype***: an individual's habitual preference for the timing of their daily activities, particularly (but not limited to) sleep and wake cycles.
- ***Circadian amplitude***: the magnitude or extent of variation, defined as the difference between an endogenous circadian rhythm's peak and trough.
- ***Circadian disruption***: although there is no formally accepted definition, the term circadian disruption is typically used to include a) atypical timing of the central pacemaker relative to external time due to phase advance or delay, or inability of the circadian system to entrain to environmental cues; b) misalignment between the timing of the central pacemaker in the SCN with peripheral oscillators elsewhere in the body, and c) reduction in amplitude of physiological rhythms.
- ***Circadian Locomotor Output Cycles Kaput (CLOCK)***: gene encoding the CLOCK transcription factor, which interacts with other proteins, including BMAL1 (Brain and Muscle ARNT-Like 1), to form the "CLOCK-BMAL1" complex. This complex binds to "E-box" elements of DNA to activate the transcription of other genes involved in the circadian clock mechanism.
- ***Circadian phase***: the relative angular displacement between a periodic quantity (e.g. the peak or the trough of the melatonin profile) and a reference angle (e.g. clock time). See also: phase angle of entrainment.
- ***Circadian rhythm***: Any biological process with an endogenous, entrainable oscillation of 24 hours that is persistent under constant environmental conditions. Circadian rhythms can be synchronized to the environmental cycle by the light/dark cycle.
- ***Circadian Rhythm Sleep-Wake Disorder (CRSWD)***: a group of sleep disorders characterized by a mismatch between an individual's sleep-wake timing from that which is desired or required by social or occupational demands, and is associated with sleep disturbances and disruption in daily functioning.
- ***Dim Light Melatonin Onset (DLMO)***: the onset of melatonin secretion when individuals are under dim light (typically < 5 lux) exposure. DLMO helps determine whether an individual is entrained (synchronized) to a 24-h light/dark cycle and for assessing phase delays or advances of rhythms in entrained individuals.
- ***Diurnal (24-hour, daily or nycthemeral) rhythms***: a rhythm in physiology or behaviour occurring over the 24-h light/dark cycle. When a rhythm is observed in the context of an environmental (e.g. light/dark) or behavioural (e.g. rest-activity) cycle, it is virtually impossible to tease apart whether daily rhythms are endogenously generated, or arise as a consequence of masking by behavioural/environmental influences.
- ***Electroencephalogram (EEG)***: a measure of brain electrical activity, using electrodes placed on the scalp.
- ***Entrainment***. active process of synchronization of an oscillator to a zeitgeber. Entrainment results in a stable phase relationship between the oscillator and the zeitgeber.
- ***Hypersomnia***: a sleep disorder characterized by excessive daytime sleepiness and an increased need for sleep.
- ***Insomnia***: difficulty in initiating or maintaining sleep, associated with distress and daytime dysfunction.
- ***Intrinsically photosensitive retinal ganglion cells (ipRGCs)***: a type of photoreceptor in the ganglion cell layer of the retina, involved in non-image-forming visual responses to light, and projecting to the SCN, thalamus and hypothalamic targets.
- ***NREM sleep***: non-Rapid Eye Movement sleep, comprising sleep stages N1 – N3, each characterized by a unique polysomnographic profile.
- ***Peripheral oscillators***: biological clocks located in cells in organs and tissues distributed throughout the body, and displaying circadian rhythmicity.
- ***Period (PER)***: in mammals, including humans, there are three PER core clock genes: PER1, PER2, and PER3. During the circadian cycle, the PER proteins accumulate at night and decrease during the day. This oscillation of PER proteins is critical for maintaining the rhythmicity of the circadian clock.
- ***Phase angle of entrainment***: the relationship between the timing of two entrained oscillators. In chronobiology, this is often used to describe the relative time difference between the central circadian clock (often estimated in humans by the dim light melatonin onset) and the timing of an external time cue (i.e. zeitgeber) or behaviour (e.g., bedtime).

66

- ***Polysomnography***: a procedure that utilizes electroencephalogram, electro-oculogram, electromyogram, electro-cardiogram, and pulse oximetry, as well as airflow and respiratory effort, to evaluate for underlying causes of sleep disturbances.
- ***Rapid Eye Movement (REM) sleep***: Sleep stage characterized by rapid and involuntary movements of the eyes and high-frequency brain activity, similar to wakefulness.
- ***Sleep spindles***: brief bursts of brainwave activity during stage 2 NREM sleep, lasting 1-2 seconds and are named after their spindle-like appearance on the EEG.
- ***Slow wave sleep (SWS)***: low-frequency, high-amplitude EEG activity known as delta waves, typically observed during NREM stage N3.
- ***Shift work***: work schedule outside the traditional 9:00 AM – 5:00 PM day. It can involve evening or night, early morning, and rotating shifts.
- ***Social jet lag***: a term used to describe the discrepancy between a person's sleep-wake timing and their socially imposed schedule, particularly during workdays and weekends.
- ***Suprachiasmatic nucleus (SCN)***: a cluster of neurons located in the hypothalamus, just superior to the optic chiasm, that plays a crucial role in regulating the body's circadian rhythm, also known as the "central pacemaker".
- ***Zeitgeber***: a synchronising stimulus capable of resetting a self-sustaining oscillation. The light/dark (LD) cycle is the most important zeitgeber for the circadian clock.

Box 2: Key gaps and opportunities for future research

1. The intricate interactions among sleep-circadian function, mood, physical and social activity, light exposure, eating, and medication, remain to be established. To capture this complexity, we endorse an integrated research agenda which incorporates measures from both sleep and wakefulness over the 24-hour cycle, with greater emphasis on the effects of waking behaviours on sleep and circadian rhythms, and vice versa.
2. A key opportunity exists for greater theoretical and practical integration of chronobiology with sleep science. The development of novel approaches to assessing circadian phase at scale, using less invasive point-of-care tests, will be central to this ambition.
3. The field has been limited by studies of small, heterogenous and sometimes poorly defined samples, using a wide range of outcome measures that limit the ability to make comparisons. Employing harmonised parameters and constructs across studies and research groups is likely to aid synthesis of findings.
4. Sleep and circadian disturbances are a transdiagnostic feature of many mental disorders. It has been hypothesized that the pathways by which sleep-circadian disturbance influence mental disorder are shared and generalizable across diagnoses, with the corollary that a single sleep-circadian intervention would benefit both sleep and mental health symptoms, across multiple disorders. This hypothesis requires further investigation, through transdiagnostic studies which delineate mechanisms and treatments that are common to all disorders, from those which are diagnosis-specific.
5. At which points in the developmental trajectory do sleep-circadian disruptions play a role in the genesis and maintenance of mental disorder, and are there critical windows of vulnerability in which to focus intervention? What are the effects of chronic sleep-circadian disruption, including increased variability in sleep timing, on mental health? Studies with a greater focus on within and between-person, longitudinal changes in sleep-circadian and mental health variables will help to address these questions.
6. What are the genetic, neurobiological and psychological mechanisms underlying vulnerability to sleep and circadian disruption on mental health?
7. The field has focused primarily on insomnia, even though most individuals with mental disorder have two or more co-morbid sleep disorders. Although insomnia is clearly a core disturbance, greater consideration of its interaction with other sleep disorders is necessary.

Citation diversity statement. Recent work in several fields of science has identified a bias in citation practices such that papers from women and other minority scholars are under-cited relative to the number of such papers in the field. Here we sought to proactively consider choosing references that reflect the diversity of the field in thought, form of contribution, gender, race, ethnicity, and other factors. First, we obtained the predicted gender of the first and last author of each reference by using databases that store the probability of a first name being carried by a woman. By this measure and excluding self-citations to the first and last authors of our current paper), our references contain 8.41% woman(first)/woman(last), 19.14% man/woman, 19.92% woman/man, and 52.52% man/man. This method is limited in that a) names, pronouns, and social media profiles used to construct the databases may not, in every case, be indicative of gender identity, and b) it cannot account for intersex, non-binary, or transgender people. Second, we obtained the predicted racial/ethnic category of the first and last author of each reference by databases that store the probability of a first and last name being carried by an author of color (11, 12). By this measure (and excluding self-citations), our references contain 6.78% author of color (first)/author of color(last), 12.98% white author/author of color, 15.71% author of color/white author, and 64.53% white author/white author. This method is limited in that a) names and Florida Voter Data to make the predictions may not be indicative of racial/ethnic identity, and b) it cannot account for Indigenous and mixed-race authors or those who may face differential biases due to the ambiguous racialization or ethnicization of their names. We look forward to future work that could help us to better understand how to support equitable practices in science.

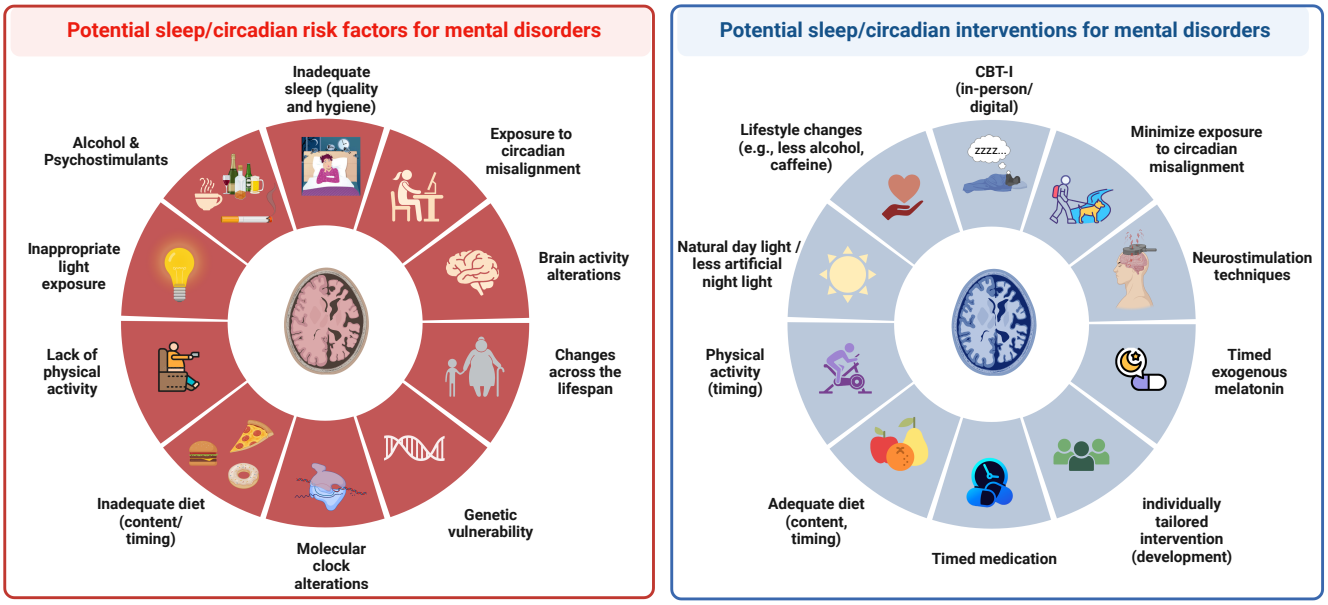

Fig. S1. Framework of sleep-circadian risk factors and interventions in psychiatric disorders. **Left:** Multiple sleep-circadian factors are likely to contribute the onset and maintenance of psychiatric disorders, including mis-timed light exposure, sedentary behaviours, meals consumed later in the day, and poor sleep hygiene. **Right:** Because many of these factors are modifiable, interventions aimed at minimising sleep and circadian disruption may show promise in preventing and treating mental disorders. While these sleep/circadian interventions are promising, further research is required to accelerate translation to patient populations. This is due to most of these laboratory studies being conducted in healthy participants, their limited sample size and the need for randomised controlled trials in patients with mental health conditions to determine magnitude of effect.

Table S1. Prevalence of sleep disorders, and objectively determined sleep and circadian abnormalities from case-control studies, in unipolar depression, anxiety disorder, bipolar disorder (mania, euthymic, or depressed phases), early psychosis/first episode populations, and schizophrenia. Sleep parameters included polysomnography, circadian biomarkers, and actigraphy (including amplitude, synchronization, sensitivity, phase and regularity of the rest-activity rhythm). Only statistically significant effects are included, and ↑ denotes an increase and ↓ indicates a decrease in sleep-circadian parameter relative to the healthy controls.

	Unipolar depression	Anxiety disorder	Bipolar Disorder	Early Psychosis*	Schizophrenia
			Prevalence and characteristics of sleep disorders		
Insomnia	14% (12) 49% (13) 59% (14)	24% (12)	*Manic*: 69-99% (15) *Euthymic*: 2-50% (14) *Depressed*: 62% (14)	48% (16) 50% (17)	7.9 – 23% (18) 26% (19) 27% (16) 29% (20) 44% (21)
Hypersomnia	9.9% (12) 7.5% (14) 14% (13)	28% (12)	*Euthymic*: 25% (22) *Depressed*: 38-78% (22) 2% (14)	23% (17)	32% (23)
CRSWD	-	-	32.4% (24)	8.3% (17)	-
Nightmare disorder	↑ Nightmare frequency(25) ↑ Suicidality(25)	-	-	48% (17) ↑ Nightmare frequency (25) ↑ Nightmare distress (25)	55% (26) 9% (27)
PSQI (28)	↑ (29)	↑ (30)	↑ (31)	↑ (16, 32)	↑ (16)
			Sleep and circadian measures		
Polysomnography	↑ REM % ↑ REM density ↑ REM duration ↓ REM latency ↓ REMOL ↑ REM pressure ↓ SE ↑ SOL ↓ SWA ↓ SWS ↓ TST ↑ WASO ↓ Continuity ↓ Depth (33, 34)	↓ REM% ↑ REM latency ↑ REM pressure ↑ N2 ↓ SE ↑ SOL ↓ SWS ↓ TST ↑ WASO ↓ Continuity ↓ Depth (33–36)	*Manic*: ↓ REMOL ↓ TST ↑ WASO (15) *Euthymic*: ↑ N1 (37) *Depressed*: ↓ N3 ↑ REM density ↓ REMOL (38)	↑ N1 ↓ SE ↑ SOL ↓ TST ↑ WASO (16) FE-P ↓ SE ↑ SOL ↓ TST ↑ WASO (32)	↑ arousals ↓ REMOL ↓ SE ↑ SOL ↑ WASO ↓ Continuity ↓ Depth (16, 33, 34)
Actigraphic sleep estimates	Delayed sleep and wake times ↓ Duration longest sleep bout ↑ naps ↓ SE ↓ sleep duration ↑ variability in bedtime and sleep duration ↑ WASO (39, 40)	Delayed sleep and wake times ↓ duration longest sleep bout ↑ naps ↓ SE ↑ variability in bedtime and sleep duration ↑ WASO (40)	*Euthymic*: Delayed sleep and wake times ↓ Duration longest sleep bout ↑ naps ↓ SE ↑ SOL ↑ TIB ↓ TST ↑ Variability in bedtime and sleep duration ↑ WASO (37, 40–42)	Delayed sleep and wake times ↓ Duration longest sleep bout ↓ SE ↑ WASO ↑ Naps ↑ Variability in bedtime and sleep duration (40, 43)	Delayed sleep and wake times ↑ Sleep duration ↓ Duration longest sleep bout ↓ SE ↑ WASO ↑ Naps ↑ Variability in bedtime and sleep duration (40, 42)
Actigraphic rest-activity profiles	↓ Daytime activity ↓ IS ↑ IV ↑ Nighttime activity ↓ RA (44–46)	↓ IS ↑ IV (46)	*Manic:* ↓ Amplitude ↑ Nighttime activity ↑ Daytime activity (47) *Euthymic*: ↓ Daytime activity(41, 42) *Depressed*: ↓ Daytime activity (48)	↓ IS ↑ IV (49, 50)	↓ Daytime activity ↑ IS ↓ IV (42, 51)
Circadian biomarkers	↓ Amplitude ↑ Desynchronisation ↓ Melatonin suppression ↑ Phase angle(52–54)	-	*Manic*: ↓ Melatonin concentrations Phase advance (55, 56) *Euthymic*: ↓ Melatonin concentrations Phase delay (56) *Depressed*: ↓ Amplitude ↑ Desynchronisation Phase delay ↓ Melatonin concentrations (55, 56)	-	↑ Misalignment ↓ Melatonin amplitude ↑ Phase angle (57–59)

CRSWD: circadian rhythm sleep-wake disorer; PSQI: Pittsburgh sleep quality index (28); IS: Interdaily Stability; IV: Intradaily Variability; RA: Relative Amplitude; TST: total sleep time; TIB: time in bed; WASO: wake after sleep onset; REMOL: REM sleep onset latency; SOL: sleep onset latency; SE: sleep efficiency; SWA: slow wave activity; SWS: slow wave sleep.

* Early psychosis includes ultra-high risk, prodromal and first-episode psychosis populations.

References

1. DJ Buysse, Sleep health: can we define it? does it matter? *Sleep* **37**, 9–17 (2014).
2. BE Jones, Arousal and sleep circuits. *Neuropsychopharmacology* **45**, 6–20 (2020).
3. T Porkka-Heiskanen, et al., Adenosine: A Mediator of the Sleep-Inducing Effects of Prolonged Wakefulness. *Science* **276**, 1265–1268 (1997).
4. N Meyer, AG Harvey, SW Lockley, DJ Dijk, Circadian rhythms and disorders of the timing of sleep. *The Lancet* **400**, 1061–1078 (2022).
5. F Rijo-Ferreira, JS Takahashi, Genomics of circadian rhythms in health and disease. *Genome Med* **11**, 82 (2019).
6. SBS Khalsa, ME Jewett, C Cajochen, CA Czeisler, A phase response curve to single bright light pulses in human subjects. *J. Physiol.* **549**, 945–952 (2003).
7. DJ Dijk, CA Czeisler, Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* **15**, 3526–38 (1995).
8. AS Lazar, ZI Lazar, DJ Dijk, Circadian regulation of slow waves in human sleep: Topographical aspects. *NeuroImage* **116**, 123–134 (2015).
9. N Santhi, et al., Sex differences in the circadian regulation of sleep and waking cognition in humans. *Proc. Natl. Acad. Sci. United States Am.* **113**, E2730–E2739 (2016).
10. DG Beersma, MC Gordijn, Circadian control of the sleep-wake cycle. *Physiol. Behav.* **90**, 190–195 (2007).
11. T Deboer, MJ Vansteensel, L Détári, JH Meijer, Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat. Neurosci.* **6**, 1086–1090 (2003).
12. DE Ford, DB Kamerow, Epidemiologic Study of Sleep Disturbances and Psychiatric Disorders: An Opportunity for Prevention? *JAMA: The J. Am. Med. Assoc.* **262**, 1479–1484 (1989).
13. PA Geoffroy, et al., Insomnia and hypersomnia in major depressive episode: Prevalence, sociodemographic characteristics and psychiatric comorbidity in a population-based study. *J. Affect. Disord.* **226**, 132–141 (2018).
14. AM Soehner, KA Kaplan, AG Harvey, Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. *J. Affect. Disord.* **167**, 93–97 (2014).
15. AG Harvey, Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am. J. Psychiatry* **165**, 820–829 (2008).
16. J Bagautdinova, et al., Sleep Abnormalities in Different Clinical Stages of Psychosis: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **80**, 202–210 (2023).
17. S Reeve, B Sheaves, D Freeman, Sleep disorders in early psychosis: Incidence, severity, and association with clinical symptoms. *Schizophr Bull* **45**, 287–295 (2019).
18. D Batalla-martín, et al., Insomnia in schizophrenia patients: Prevalence and quality of life. *Int. J. Environ. Res. Public Heal.* **17**, 1–12 (2020).
19. YT Xiang, et al., Prevalence and correlates of insomnia and its impact on quality of life in chinese schizophrenia patients. *Sleep* **32**, 105–9 (2009).
20. CL Hou, et al., Prevalence of Insomnia and Clinical and Quality of Life Correlates in Chinese Patients With Schizophrenia Treated in Primary Care. *Perspectives Psychiatr. Care* **53**, 80–86 (2017).
21. LB Palmese, et al., Sleep patterns of individuals with schizophrenia. *Schizophr Bull* **37**, 277 (2011).
22. KA Kaplan, J Gruber, P Eidelman, LS Talbot, AG Harvey, Hypersomnia in inter-episode bipolar disorder: Does it have prognostic significance? *J. Affect. Disord.* **132**, 438–444 (2011).
23. P Sharma, Excessive Daytime Sleepiness in Schizophrenia: A Naturalistic Clinical Study. *J. Clin. Diagn. Res.* **10**, 10–12 (2016).
24. Y Takaesu, et al., Prevalence of circadian rhythm sleep-wake disorders and associated factors in euthymic patients with bipolar disorder. *PLoS ONE* **11**, e0159578 (2016).
25. MA Akkaoui, M Lejoyeux, MP D'ortho, PA Geoffroy, Nightmares in patients with major depressive disorder, bipolar disorder, and psychotic disorders: A systematic review. *J. Clin. Medicine* **9**, 1–26 (2020).
26. B Sheaves, J Onwumere, N Keen, D Stahl, E Kuipers, Nightmares in patients with psychosis: The relation with sleep, psychotic, affective, and cognitive symptoms. *Can. J. Psychiatry* **60**, 354–361 (2015).
27. SX Li, et al., Sleep disturbances and suicide risk in an 8-year longitudinal study of schizophrenia-spectrum disorders. *Sleep* **39**, 1275–1282 (2016).
28. DJ Buysse, CF Reynolds, TH Monk, SR Berman, DJ Kupfer, The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* **28**, 193–213 (1989).
29. Y Hayashino, et al., Association between number of comorbid conditions, depression, and sleep quality using the Pittsburgh Sleep Quality Index: Results from a population-based survey. *Sleep Medicine* **11**, 366–371 (2010).
30. AL Bush, et al., The Pittsburgh Sleep Quality Index in older primary care patients with generalized anxiety disorder: Psychometrics and outcomes following cognitive behavioral therapy. *Psychiatry Res.* **199**, 24–30 (2012).
31. A Slyepchenko, et al., Association of functioning and quality of life with objective and subjective measures of sleep and biological rhythms in major depressive and bipolar disorder. *Aust. New Zealand J. Psychiatry* **53**, 683–696 (2019).
32. C Dondé, et al., Sleep disturbances in early clinical stages of psychotic and bipolar disorders: A meta-analysis. *Aust. New Zealand J. Psychiatry* **56**, 1068–1079 (2022).
33. RM Benca, WH Obermeyer, RA Thisted, JC Gillin, Sleep and Psychiatric Disorders: A Meta-analysis. *Arch. Gen.*

Psychiatry **49**, 651–668 (1992).
34. C Baglioni, et al., Sleep and mental disorders: A meta-analysis of polysomnographic research. *Psychol. Bull.* **142**, 969–990 (2016).
35. GN Papadimitriou, P Linkowski, Sleep disturbance in anxiety disorders. *Int. review psychiatry* **17**, 229–236 (2005).
36. RC Cox, BO Olatunji, Sleep in the anxiety-related disorders: A meta-analysis of subjective and objective research. *Sleep Medicine Rev.* **51**, 101282 (2020).
37. TH Ng, et al., Sleep-wake disturbance in interepisode bipolar disorder and high-risk individuals: A systematic review and meta-analysis. *Sleep Medicine Rev.* **20**, 46–58 (2015).
38. AM Soehner, KA Kaplan, AG Harvey, Insomnia comorbid to severe psychiatric illness. *Sleep Medicine Clin.* **8**, 361–371 (2013).
39. Y Tazawa, et al., Actigraphy for evaluation of mood disorders: A systematic review and meta-analysis. *J Affect. Disord* **253**, 257–269 (2019).
40. M Wainberg, et al., Association of accelerometer-derived sleep measures with lifetime psychiatric diagnoses: A cross-sectional study of 89,205 participants from the uk biobank. *PLOS Medicine* **18**, e1003782 (2021).
41. PA Geoffroy, et al., Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatr Scand* **131**, 89–99 (2015).
42. N Meyer, et al., Sleep and circadian rhythm disturbance in remitted schizophrenia and bipolar disorder: A systematic review and meta-analysis. *Schizophr Bull* **46**, 1126–43 (2020).
43. J Scott, et al., A systematic review and meta-analysis of sleep and circadian rhythms disturbances in individuals at high-risk of developing or with early onset of bipolar disorders. *Neurosci. Biobehav. Rev.* **135**, 104585 (2022).
44. C Burton, et al., Activity monitoring in patients with depression: A systematic review. *J. Affect. Disord.* **145**, 21–28 (2013).
45. RT Krafty, et al., Measuring Variability in Rest-Activity Rhythms from Actigraphy with Application to Characterizing Symptoms of Depression. *Stat. biosciences* **11**, 314–333 (2019).
46. AI Luik, et al., 24-hour activity rhythm and sleep disturbances in depression and anxiety: A population-based study of middle-aged and older persons. *Depress. Anxiety* **32**, 684–692 (2015).
47. P Salvatore, et al., Circadian activity rhythm abnormalities in ill and recovered bipolar I disorder patients. *Bipolar Disord.* **10**, 256–265 (2008).
48. K Krane-Gartiser, TEG Henriksen, G Morken, A Vaaler, OB Fasmer, Actigraphic assessment of motor activity in acutely admitted inpatients with bipolar disorder. *PLoS ONE* **9**, e89574 (2014).
49. J Castro, et al., Circadian rest-activity rhythm in individuals at risk for psychosis and bipolar disorder. *Schizophr. Res.* **168**, 50–55 (2015).
50. JR Lunsford-Avery, et al., Adolescents at clinical-high risk for psychosis: Circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. *Schizophr. Res.* **189**, 37–42 (2017).
51. JO Berle, ER Hauge, KJ Oedegaard, F Holsten, OB Fasmer, Actigraphic registration of motor activity reveals a more structured behavioural pattern in schizophrenia than in major depression. *BMC Res. Notes* **3**, 149 (2010).
52. A Germain, DJ Kupfer, Circadian rhythm disturbances in depression. *Hum. Psychopharmacol.* **23**, 571–585 (2008).
53. P Courtet, E Olié, Circadian dimension and severity of depression. *Eur. Neuropsychopharmacol.* **22**, S476–S481 (2012).
54. EM McGlashan, MY Coleman, P Vidafar, AJ Phillips, SW Cain, Decreased sensitivity of the circadian system to light in current, but not remitted depression. *J. Affect. Disord.* **256**, 386–392 (2019).
55. JH Moon, et al., Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder. *EBioMedicine* **11**, 285–295 (2016).
56. MJ McCarthy, et al., Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology. *Bipolar Disord.* **24**, 232–263 (2022).
57. G Anderson, M Maes, Melatonin: An overlooked factor in schizophrenia and in the inhibition of anti-psychotic side effects. *Metab. Brain Dis.* **27**, 113–119 (2012).
58. TC Delorme, LK Srivastava, N Cermakian, Are Circadian Disturbances a Core Pathophysiological Component of Schizophrenia? *J. Biol. Rhythm.* **35**, 325–339 (2020).
59. K Wulff, DJ Dijk, B Middleton, RG Foster, EM Joyce, Sleep and circadian rhythm disruption in schizophrenia. *Br. J. Psychiatry* **200**, 308–316 (2012).