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Guest Editorial

# Chronopsychiatry

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This editorial summarises the clinical relevance of 'chronopsychiatry', defined as the interface between circadian science and mental health science. Chronopsychiatry represents a move towards time-variable perspectives on neurobiology and symptoms, with a greater emphasis on chronotherapeutic interventions.

**Keywords**
Sleep; circadian; depression; bipolar disorder; psychosis.



Chronopsychiatry can be defined as the pathophysiological and clinical interface between circadian rhythms and mental illness. It draws on multiple disciplines, encompassing neuroscience, endocrinology, psychology, psychiatry and public health. For diagnoses including major depression, psychosis, bipolar disorder, dementia and neurodevelopmental disorders, abnormalities of sleep and circadian function are strongly implicated in both physiological mechanisms and treatment outcomes. Chronopsychiatric research and practice may therefore represent an important paradigm shift for psychiatry, representing a move away from the consideration of 'one-size-fits-all' static processes towards individual, dynamic and time-variable perspectives on the interaction between neurobiology, environment, behaviour and symptoms.

## The circadian system: connecting the environment with physiology and behaviour

Endogenous, self-sustaining 24 h (circadian) rhythms are found across almost all forms of life (with some exceptions in mammals, birds and insects driven by polar extremes and/or feeding, social or reproductive behaviours). Circadian oscillations exist at multiple molecular and cellular levels, enabling organisms to anticipate periodic changes in the environment and thereby synchronise the timing of physiology and behaviour to the 24 h day. Circadian rhythms play a fundamental role in all aspects of our physiology, but via interaction with sleep and arousal systems, the circadian system plays a critical role in regulating the timing of sleep. Regular sleep patterns are vital for brain development and plasticity, cognitive function, emotional regulation, immunity and metabolism. Circadian timing varies with age and contributes to changes in the timing of sleep across the lifespan: sleep and circadian timing become progressively later over adolescence ('night owls') and then typically advance again in adulthood and into older ages ('morning larks').

Healthy circadian function requires internal clocks throughout the body to be aligned both with one another and with the environment, promoting an appropriately timed circadian signal. In humans, daily light exposure is the main signal by which the circadian system is synchronised to the daily 24 h day–night cycle. The timing of meals, activity and social interactions also helps to synchronise rhythms, but these factors are less potent than light. In modern society, there are now multiple environmental disruptors of circadian function, including dim daytime light, excess artificial light at night, night-time screen use (including social media), sedentary behaviour, noise pollution and irregular work patterns (shift-work and night-work). In essence, our ancient physiological mechanisms of sleep homeostasis are ill suited to modern living, and the resulting disruption can be particularly toxic for individuals with a vulnerability to mental illness.[1]

## Novel insights into the mechanisms of mental illness

Given the ubiquity of circadian biology within every physiological system, research is beginning to uncover the wide-ranging consequences of circadian disruption on mental health and the mechanisms underlying this relationship.

Shift-work (and travel across time-zones) is associated with relapse in mood disorders, suggesting that misalignment between endogenous circadian rhythms and day–night cycles contributes to mood dysregulation. In addition, internal desynchrony between biological clocks in different organs – for example, the central pacemaker in the suprachiasmatic nucleus and clocks in the liver – may contribute to the adverse metabolic consequences of shift-work. Delayed sleep-wake and/or circadian timing is associated with depression, bipolar disorder, obsessive–compulsive disorder and attention-deficit hyperactivity disorder. In dementia, neurodegeneration of the central circadian pacemaker contributes directly to irregular sleep-wake patterns.

The association between seasonal variation in day length and mental ill health illustrates the fundamental role of light on mental well-being. For example, individuals with unipolar depression and bipolar disorder are more likely to develop depressive episodes in autumn and winter months, correlated with a shorter photoperiod (daylength). Conversely, the risk of manic relapse in bipolar disorder is elevated in spring and summer months. There is also growing evidence that inter-individual differences in the sensitivity of the circadian system to light may increase vulnerability for sleep and mood disturbance. Indeed, super-sensitivity to light may be a feature of bipolar disorder, leading to increased risk of circadian disruption with even relatively minor changes in environmental light.

The precise mechanisms that link circadian disruption and mental illness are not yet fully understood.[2] There is some evidence of shared genetic vulnerability between sleep/circadian phenotypes (such as evening chronotype) and conditions such as bipolar disorder and major depression, and genetic risk factors for schizophrenia may be associated with abnormalities of sleep structure. However, more work is needed in this area, not least because genetic studies have been limited by incomplete diagnostic and sleep/circadian phenotyping, small sample sizes and cross-sectional designs. In the area of clinical trials, factors such as timing of medication dose, season and latitude are typically not considered.

It is well recognised that chronic sleep deprivation has a negative impact on mood, emotion regulation and our perception of both positive and negative events. At the most extreme level, total sleep deprivation for four days will lead to psychotic symptoms (hallucinations and paranoid delusions) in almost everyone. The most likely mechanism connecting sleep disruption and emotional dysregulation is a combination of 'top-down' cortical hyperarousal and



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abnormal 'bottom-up' brainstem arousal. This may be particularly important for children and adolescents, many of whom are highly sensitive to the adverse effects of sleep and circadian disruption. In fact, the vast majority of adolescents living in countries such as the UK now have chronic sleep deprivation (a combination of their late chronotype and the need to wake early on schooldays). Despite this, the narrative around the current spike in adolescent mental ill health only rarely addresses sleep as a causal – and yet potentially modifiable – risk factor.

The body's immune, metabolic and cellular energy functions are all under tight circadian control and may contribute to the mechanisms by which sleep and circadian disruption causes mental health problems. However, the evidence for this so far is largely indirect. Most studies linking inflammatory and metabolic markers to psychiatric disorders have ignored important considerations of circadian (and indeed seasonal) variation in these markers, making conclusions about mechanisms tentative at best. An extra layer of complexity comes from the likelihood of developmental and age-dependent differences in the link between immune function, metabolism and mental illness. More ambitious prospective studies are needed that take a 'deep-phenotyping' approach to measuring within-day and day-to-day (and seasonal) variations in immune, metabolic and brain energy markers.

Another important but neglected area is the paucity of sleep/circadian and mental health studies from low- and middle-income countries. Almost all available evidence comes from work conducted in high-income countries and, as such, fails to account for potentially important differences in societal, familial, cultural, economic and geographical factors.

## Comorbidity between physical and mental health disorders

Sleep and circadian disruption is a core feature of many physical health problems, including obesity, type II diabetes, cardiovascular disease and chronic pain. These are all relatively common comorbidities for people with psychiatric disorders, and it is likely that circadian dysfunction plays a role in driving this comorbidity. These comorbidities also lead to disrupted sleep, establishing a vicious cycle. More research in this area could deliver improved physical health benefits for people with mental illness, as well as mental health benefits for individuals living with chronic physical health conditions and multimorbidity.

## New approaches to clinical research and treatment

What might be the implications of chronopsychiatry for future clinical practice? Chronotherapeutic interventions remain largely underused, despite a strong theoretical rationale for their use and a substantial and growing evidence base.[3] Taking mood disorders as an example, there is good evidence for several different chronotherapeutic approaches, including: light therapies, cognitive–behavioural therapy for insomnia (CBTi), sleep deprivation for depressive episodes, dark therapies for mania (such as evening light restriction and blue-light blocking glasses) and interpersonal social rhythm therapy (IPSRT) for relapse prevention in bipolar disorder.[4] In general, these interventions can be delivered alongside conventional treatments but have not yet been adopted by most practitioners and services. Chronotherapies are intuitively appealing to many patient groups, such as people with bipolar disorder, who often recognise the importance of light exposure and seasonal mood variation (and are very keen to make use of adjunctive, non-medication treatment options).

Looking ahead, technological advances are likely to lead to better research and clinical practice in the chronopsychiatry field. Research-grade and consumer-grade digital and wearable technologies are extending the reach, affordability and acceptability of measuring longitudinal sleep and rest-activity variables (as well as light exposure), within both clinical and non-clinical settings. Obtaining accurate markers of endogenous circadian function is essential to better understand the contribution of aberrant circadian phase or amplitude to a given sleep-wake phenotype. Unfortunately, these biomarkers are rarely collected in research studies, and even less so in clinical practice. Novel circadian assays and physiologically informed prediction models may help to overcome this barrier by delivering less invasive, point-of-care tests for measuring endogenous circadian rhythms. The field also needs to embrace open science practices and collaborations to improve the standardisation and analysis of circadian data, in both animal and human studies.

The importance of chronopsychiatry was recognised recently by a scoping report[5] and a major funding initiative from the Wellcome Trust, 'Integrating sleep and circadian science into our understanding and treatment of anxiety, depression and psychosis'. Similarly, the Medical Research Council have invested in a new Circadian Mental Health Network (www.circadianmentalhealth.org), which will identify research priorities and build new interdisciplinary capacity for both discovery science and future chronotherapeutic interventions.

Chronopsychiatry represents an exciting new area for psychiatric research and clinical practice. Recent investments by research funders are an important first step, but this now needs to be matched by a step-change in the awareness and training of chronopsychiatric principles and practice for health professionals, particularly psychiatrists.

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