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Review Article

Circadian Rhythm Disruption and Neurobehavioral Function: Roles of Melatonin, Spatial Memory, Motor Coordination and Feeding Behavior

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ABSTRACT

Circadian rhythms coordinate sleep–wake behavior, endocrine secretion, metabolism and neural function across the approximately 24-hour day. Disruption of the circadian system can alter cognitive performance, motor behavior, feeding patterns and melatonin secretion, although the direction and magnitude of these effects depend on species, lighting conditions, disease model and experimental protocol. This narrative review examines the molecular organization of the mammalian circadian clock, the role of the suprachiasmatic nucleus and peripheral oscillators, and mechanistic links between circadian misalignment and neurobehavioral outcomes. Particular attention is given to the Morris water maze as an assay of spatial learning, the rotarod as an assessment of motor coordination, time-dependent melatonin measurements and food-intake monitoring in rodents. Methodological considerations—including Zeitgeber-time reporting, repeated testing, motor confounding, cage-level food measurements and melatonin assay validation—are discussed. The review concludes that multimodal behavioral, endocrine and metabolic assessments can provide complementary information, but robust inferences about circadian phase or rhythm disruption require repeated sampling across the circadian cycle and appropriate experimental controls.

INTRODUCTION

Biological timing allows organisms to anticipate predictable environmental changes rather than simply respond to them. In mammals, the central circadian pacemaker in the suprachiasmatic nucleus (SCN) synchronizes distributed cellular clocks using neural, endocrine and behavioral signals [1–3]. Light is the dominant environmental timing cue for the SCN, while meal timing, physical activity and temperature can influence peripheral oscillators. Circadian misalignment can occur following irregular light exposure, shift work, sleep restriction, mistimed feeding or experimental phase shifts. These conditions can produce overlapping effects on arousal, cognition, metabolism and movement, making interpretation of behavioral tests especially dependent on the time of testing [2,4].

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The purpose of this review is to integrate mechanistic and methodological evidence relevant to circadian biology and common pharmacology endpoints, without presenting new animal data.

MATERIALS AND METHODS: NARRATIVE REVIEW APPROACH

This article is a narrative synthesis of the published literature cited below, rather than a report of new experiments. The discussion draws on foundational publications concerning molecular clocks, melatonin signaling, learning and memory, behavioral testing, feeding schedules, animal-study reporting and chronopharmacology. The original draft does not document a database search, search dates, screening criteria or formal quality assessment; therefore, no systematic-review or meta-analysis methods are claimed. No new animals or human participants were recruited for this review.

The mammalian transcription–translation feedback loop is built around CLOCK and BMAL1, which activate Period (PER1–3) and Cryptochrome (CRY1–2) transcription. PER and CRY proteins accumulate and inhibit CLOCK–BMAL1 activity, creating an oscillation that is stabilized by auxiliary pathways involving REV-ERB and ROR nuclear receptors [1,3]. Circadian clocks influence cellular metabolism, oxidative stress defenses, hormone responsiveness and gene expression.

The SCN receives photic information through retinal projections and coordinates behavioral rhythms, while peripheral clocks in the liver, adipose tissue, gastrointestinal tract and other organs respond to both central and local timing cues [2,5]. A disturbance in synchronization may alter physiological timing even when individual tissue oscillators remain functional. Accordingly, changes in a single measured hormone or behavior cannot by themselves demonstrate that the molecular clock has stopped.

Table 1: Components of the Mammalian Circadian System

Component	Principal role	Interpretive consideration
SCN	Coordinates central timing in response to light	Central phase and peripheral phase may differ
CLOCK–BMAL1	Promotes transcription of clock-associated genes	Expression at one time does not establish rhythmicity
PER–CRY	Participates in negative feedback	Requires time-resolved measurement
Peripheral clocks	Coordinate tissue-specific physiological timing	Feeding can alter peripheral alignment

MELATONIN AS A CIRCADIAN SIGNAL

Melatonin is produced principally by the pineal gland under sympathetic control and typically rises during the biological night. Its secretion provides a hormonal signal of darkness, and its timing and amplitude are influenced by photoperiod, age, light exposure, species and strain [6,7]. Melatonin acts through MT1 and MT2 receptors and has been investigated for effects on sleep timing, antioxidant signaling and neuroprotection, although experimental benefits are context-dependent [7].

In rodents, Zeitgeber time (ZT) is referenced to the external light–dark schedule: under a conventional 12:12 light–dark cycle, ZT0 is lights-on and ZT12 is lights-off. ZT2 and ZT14 therefore indicate two hours after lights-on and two hours after lights-off, respectively. These labels should not be interchanged. In nocturnal animals, the light phase is generally the rest phase and the dark phase the active phase. Two sampling times can demonstrate a day–night difference but cannot define circadian phase, period, amplitude or arrhythmicity with confidence. More extensive serial sampling, ideally alongside activity records and controlled lighting, is required for stronger rhythm-level claims.

Melatonin immunoassays require attention to sample matrix, collection timing, sensitivity, extraction procedures and standard-curve validity. Competitive ELISAs commonly produce an inverse relation between analyte concentration and signal, but the direction must be confirmed from the specific kit instructions rather than assumed [6].

Table 2: Interpretation of Melatonin Sampling

Measurement	What it may support	What it cannot establish alone
ZT2 versus ZT14	Difference between two scheduled collection times	Circadian period, amplitude or precise phase
Single melatonin concentration	Hormone concentration at sampling	Global integrity of the circadian clock
Serial time-point profile	Temporal variation under defined conditions	Mechanism without additional controls

CIRCADIAN TIMING, LEARNING AND SPATIAL MEMORY

Learning and memory depend on hippocampal and cortical networks whose synaptic plasticity, gene expression and neuromodulatory environment can vary by time of day [8,9]. Sleep loss and circadian disruption may impair acquisition, consolidation or retrieval, but these processes are not interchangeable. Behavioral performance also reflects motivation, stress responsiveness, visual function and locomotion.

The Morris water maze evaluates spatial navigation using distal cues and an escape platform [10]. Common outcomes include escape latency during acquisition, path length, swimming speed and probe-trial measures of spatial bias or platform-location memory. A lower escape latency can indicate improved task performance, but should not be interpreted as improved memory without evaluating motor and sensory confounders. Differences in swimming speed, floating, thigmotaxis or visual ability can alter latency independently of spatial learning. Testing should occur at comparable ZT across groups, with consistent lighting and environmental cues. Repeated training trials and animal-level dependence should be addressed statistically [10,11].

CIRCADIAN TIMING AND MOTOR COORDINATION

Motor performance varies with arousal, fatigue, muscle function, coordination and motivation, all of which may be influenced by time of day. The rotarod apparatus is widely used to evaluate balance, coordination and motor learning in rodents [12]. Latency to fall is the common outcome, but it is affected by apparatus speed, acceleration profile, training, body weight and trial cutoffs. Fixed-speed and accelerating protocols should not be pooled as though they were equivalent.

A rotarod result is not a direct measure of cognition or circadian rhythm. However, it is valuable when interpreted alongside a spatial-memory task: a disease model or treatment that changes motor ability may affect water-maze escape latency even without altering memory. Habituation, standardized trial spacing and blinded assessment can improve interpretability. Repeated trials should be analyzed with methods appropriate to within-animal correlation [12].

Table 3: Neurobehavioral Endpoints and Potential Confounders

Assay	Typical endpoint	Important confounders
Morris water maze	Escape latency, path length, probe performance	Swimming speed, vision, stress, motivation
Rotarod	Latency to fall	Training, acceleration, body mass, fatigue
Activity monitoring	Temporal locomotor pattern	Handling, cage conditions, light exposure

FEEDING BEHAVIOR, METABOLISM AND PERIPHERAL CLOCKS

Feeding and fasting cycles are powerful temporal signals for peripheral circadian oscillators. Mistimed food access can shift liver and other peripheral rhythms relative to the SCN, contributing to internal desynchrony [5,13]. Circadian misalignment may also alter appetite-related hormones, energy expenditure and glucose homeostasis [4,14]. Conversely, feeding schedules can reshape

rhythmic metabolic processes, creating a bidirectional relationship between clocks and nutrition.

Food intake should be measured in a way that reflects the true experimental unit. When mice are group-housed and food disappearance is measured per cage, the cage—not each mouse—is usually the independent unit. Spillage, hoarding, bedding contamination, water availability, body weight and the timing of measurement must be considered. A single 24-hour total may conceal substantial changes in the distribution of intake between light and dark phases. Recording feeding by phase or using automated monitoring can better characterize temporal feeding behavior [13,14].

Table 4: Feeding Measurements in Circadian Experiments

Approach	Useful information	Limitation
24-hour food disappearance	Total apparent consumption	May obscure light–dark redistribution
Light-phase/dark-phase intake	Timing of feeding	Spillage and timing consistency matter
Cage-level measurement	Cage food disappearance	Cage is generally the experimental unit

INTEGRATING BEHAVIORAL, ENDOCRINE AND METABOLIC ENDPOINTS

Combining spatial-memory, motor, endocrine and feeding measures can help distinguish possible pathways of impairment. For example, a change in water-maze escape latency together with a rotarod deficit raises the possibility of motor confounding. A change in night-time melatonin concentration may reflect altered pineal output or environmental lighting rather than necessarily a global failure of clock regulation. Likewise, an altered daily food-intake total does not establish a shift in feeding phase.

Interpretation is strongest when supported by synchronized sampling schedules, locomotor-activity rhythms, sleep or rest measures, body-weight trajectories and molecular clock markers where feasible. Candidate markers include BMAL1, PER, CRY and clock-controlled metabolic genes, measured across multiple time points rather than at a single sampling hour [1,3]. Mechanistic claims require interventions or convergent evidence beyond correlations among endpoints.

EXPERIMENTAL DESIGN AND STATISTICAL CONSIDERATIONS

Animal experiments should specify species, strain, sex, age, housing conditions, photoperiod, light intensity, acclimatization, sampling ZT, randomization, blinding and predefined exclusions. The ARRIVE 2.0 guidelines provide a useful framework for transparent reporting [15]. Experimental schedules should avoid testing one group consistently earlier than another. Night-phase procedures require lighting that minimizes unintended circadian effects.

For independent treatment groups measured at one time, one-way ANOVA with prespecified multiplicity-adjusted comparisons may be appropriate when assumptions are met. Designs involving group and sampling time may require factorial models, and repeated measurements in the same animal require paired or mixed-effects approaches. Normality, variance heterogeneity and the unit of replication should be considered before selecting tests. Statistical significance alone does not establish biological importance; effect sizes, confidence intervals and assay reliability are also informative. No original statistical results are reported in this review.

THERAPEUTIC AND CHRONOPHARMACOLOGICAL IMPLICATIONS

Circadian-informed approaches include stable light–dark schedules, appropriately timed feeding, sleep regularity and interventions directed at melatonin signaling or clock-related pathways. Chronopharmacology examines how dosing time can affect pharmacokinetics, target sensitivity and toxicity [16]. Nevertheless, results from nocturnal rodents cannot be directly transferred to daytime human behavior without accounting for species-specific phase relationships. Claims that an intervention restores a circadian rhythm should be supported by longitudinal rhythm metrics rather than isolated time-point differences.

LIMITATIONS AND FUTURE DIRECTIONS

The literature spans diverse models and protocols, limiting direct comparison across studies. Common challenges include sparse sampling, lack of activity monitoring, inconsistent ZT notation, inadequate control for locomotor ability and pseudo-replication in feeding studies. Future work should integrate longitudinal actigraphy or wheel-running, multi-time-point hormone profiles, phase-resolved feeding measurements and appropriately controlled neurobehavioral testing. Sex-specific and strain-specific responses deserve attention. Where possible, circadian outcomes should be evaluated with rhythm-specific analytical methods rather than simple comparisons of daytime and night-time means.

CONCLUSION

Circadian timing connects endocrine signals, cognitive function, motor performance and metabolic behavior through coordinated central and peripheral clocks. Melatonin measurements, Morris water maze testing, rotarod performance and food-intake monitoring offer complementary perspectives, but each endpoint has important interpretive limitations. Carefully standardized Zeitgeber timing, appropriate statistical design and multimodal evidence are essential for distinguishing circadian dysregulation from changes in general health, activity or motivation. A mechanistically grounded, methodologically rigorous approach can strengthen future pharmacological investigations of circadian-related neurobehavioral dysfunction.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest regarding the publication of this review article.

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