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PERSPECTIVES

From Wings to Wellness: A Research Agenda Inspired by Migratory Bird Adaptations for Sleep and Circadian Medicine

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Abstract: Migratory birds demonstrate remarkable temporal plasticity, adapting their circadian rhythms and sleep patterns to meet the demands of long-distance migration. This perspective explores how insights from avian temporal adaptations could inform novel research directions in human sleep and circadian medicine. Birds' ability to maintain precise temporal organization through multiple coordinated oscillators, particularly during migratory periods, provides a valuable framework for understanding circadian flexibility. Drawing from recent advances in avian chronobiology, we propose several research priorities for human applications, including biomarker-guided chronotherapy, circuit-specific interventions, and optimization of environmental cue timing. We explore how birds' sophisticated control of sleep architecture and metabolic regulation during migration might inspire new approaches to managing circadian disruptions in humans. Neuroimaging studies of human temporal adaptability, guided by avian insights, could reveal network-level mechanisms underlying circadian plasticity. Of particular interest is the parallel between avian unihemispheric sleep and human hemispheric asymmetry during sleep, suggesting the evolutionary conservation of adaptive sleep mechanisms. While acknowledging the fundamental differences between avian and human circadian systems, we outline specific research directions that could translate avian temporal adaptability principles into therapeutic strategies for circadian disorders. While these avian-inspired hypotheses require rigorous validation, and some may not prove viable, embracing creative exploration remains essential for advancing our understanding of human circadian biology and guiding the development of novel therapeutic approaches.

Keywords: temporal plasticity, unihemispheric sleep, circadian rhythms, sleep disorders, neuroplasticity, translational research

Introduction

This perspective aims to explore potential research directions in human sleep and circadian medicine inspired by the remarkable temporal plasticity observed in migratory birds. Drawing from avian sleep and circadian adaptations, we attempt to identify promising areas for investigation in human studies, particularly focusing on molecular mechanisms and neural circuits that might be relevant to human circadian disorders.[1] While recognizing the fundamental differences between avian and human circadian systems, we propose a few research ideas that could advance our understanding of temporal regulation in humans and potentially inform future therapeutic strategies.

The sophisticated endogenous cellular mechanisms of migratory birds respond precisely to environmental cues, particularly the light/dark cycle, making them invaluable models for understanding temporal regulation.[2] These internal timekeeping systems orchestrate critical physiological processes, from sleep-wake cycles to metabolic functions, demonstrating remarkable flexibility during migration periods that could inform novel therapeutic approaches in human chronobiology.[3,4] Representative migratory bird species discussed in this perspective are shown in Figure 1.

Avian adaptations for sleep and circadian rhythms provide valuable insights into human circadian medicine, despite the phylogenetic distance, due to shared fundamental circadian mechanisms conserved through evolution.[5] While current human circadian research faces limitations such as ethical constraints and challenges in longitudinal monitoring, recent technological advances like wearable devices and machine learning algorithms offer new opportunities for continuous monitoring and personalized interventions.[6,7] Environmental factors, including light pollution and irregular schedules,

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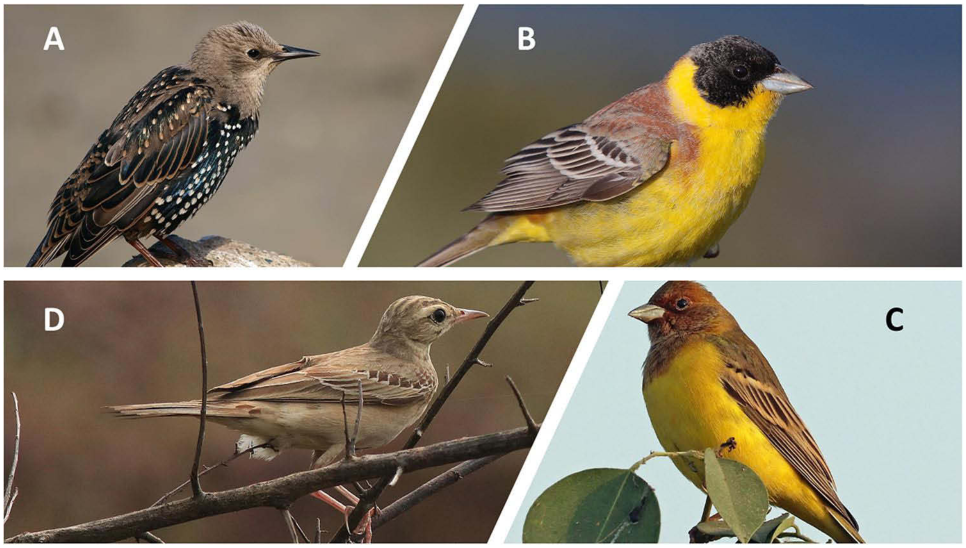

Figure 1 Avian Models for Understanding Temporal Plasticity in Circadian Systems Representative migratory bird species discussed in this perspective: (**A**) European Starling (Sturnus vulgaris), demonstrating rapid transitions between diurnal and nocturnal activity patterns; (**B**) Black-headed Bunting (Emberiza melanocephala) and (**C**) Red-headed Bunting (Emberiza bruniceps), showing distinct hypothalamic gene expression patterns during migratory states; (**D**) Tawny Pipit (Anthus campestris), exhibiting precise timing of migratory flights relative to sunset. These species exemplify specific aspects of temporal plasticity relevant to understanding circadian adaptation mechanisms.

contribute to circadian disruption in modern society, affecting miRNA-mediated regulation and various physiological processes.[8] Understanding these complex interactions is crucial for developing effective chronotherapeutic strategies and addressing the extensive reach of circadian regulation in human physiology, as revealed by recent genomic and proteomic studies.[6]

Circadian rhythm disorders represent a growing public health burden and contribute significantly to metabolic, cardiovascular, and neurological diseases in humans.[9,10] The widespread adoption of artificial lighting, irregular work schedules, and constant exposure to electronic devices have led to unprecedented disruption of natural circadian rhythms.[11] These disruptions manifest in various disorders ranging from sleep disturbances to metabolic syndrome, with annual healthcare costs exceeding billions of dollars.[12,13]

Birds represent compelling models for human circadian research despite phylogenetic distance, as both share fundamental chronobiological mechanisms. Like humans, birds possess a master circadian pacemaker that coordinates peripheral oscillators, though birds have a more complex multi-oscillatory system involving the pineal gland, retina, and hypothalamic structures.[14] Both species express highly conserved clock genes (Period, Cryptochrome, Clock, and Bmal1) that function through similar transcriptional-translational feedback loops.[14] Notably, avian cryptochromes (especially Cry4) demonstrate exceptional sensitivity to magnetic fields and blue light, potentially offering insights into human magnetoreception and photosensitivity mechanisms.[15–17] While birds exhibit more pronounced circadian entrainment to light than mammals—with light suppressing sleep almost completely without subsequent rebound[18] —both species show homeostatic sleep regulation with similar sleep architecture, including REM and non-REM phases. Birds also display robust diurnal patterns like humans, unlike many rodent models. However, important differences exist: birds possess light-sensitive extra-retinal photoreceptors and pineal melatonin production that directly entrains peripheral oscillators, whereas humans rely primarily on retinal photoreception and SCN-mediated signaling.[19,20] Additionally, birds demonstrate remarkable sleep plasticity during migration, which humans lack.[21,22] Despite these differences, the similarities in core clock mechanisms, sleep homeostasis, and diurnality make birds valuable comparative models for understanding fundamental principles of circadian biology applicable to human health.[23,24]

Recent research has revealed that disruptions in circadian rhythms can significantly impact health outcomes, affecting everything from cognitive performance to metabolic regulation.[25,26] The avian model offers a useful framework for understanding how biological clocks maintain the temporal organization of physiological processes and how their disruption might contribute to various pathological conditions in humans.

The avian sleep architecture exhibits unique characteristics that make it particularly valuable for sleep research. Unlike mammals, birds can engage in unihemispheric slow-wave sleep (USWS), allowing them to remain partially vigilant while resting, with one eye open to monitor their environment for predators.[1] This adaptation is especially crucial during long-distance migrations, as demonstrated in frigatebirds that primarily engage in unihemispheric sleep during flight.[1] This regulation involves complex interactions between molecular and neural mechanisms. The neural basis of unihemispheric sleep involves distinct patterns of activity between hemispheres, manifesting as chimera-like states where one hemisphere exhibits synchronization while the other remains desynchronized.[27] Recent molecular studies have revealed that BMAL2, a key circadian regulator, shows adaptations specifically associated with unihemispheric sleep patterns, promoting increased arousal-related gene expression in the active hemisphere.[28] The synchronization patterns between hemispheres demonstrate remarkable plasticity, allowing for rapid switching between symmetric and asymmetric states depending on environmental demands.[29]

Circadian clocks of birds show fundamental similarities to mammalian systems at the molecular level, with both groups sharing core clock components, including BMAL, Clock, Per2, Per3, Cry1, and Cry2, though birds possess some unique features in their phase relationships and light response mechanisms.[14,30,31] These cellular timekeepers coordinate various physiological processes, including neural plasticity and memory consolidation, which are essential for both avian navigation and human cognitive function.[32]

While this perspective builds on well-established findings from avian circadian and sleep research, it also proposes hypotheses that currently lack direct experimental support in humans. By identifying these gaps, the perspective aims to inspire future research and highlight areas where avian models can inform human studies. This selective integration of evidence from avian and human research can generate novel hypotheses, focusing on translational potential rather than providing an exhaustive review of the literature.

Temporal Flexibility in Migratory Birds

Migratory birds exhibit remarkable circadian plasticity, shifting seamlessly between diurnal and nocturnal activity patterns. During non-migratory periods, most songbirds adhere to strictly diurnal behaviors. However, migration induces a profound temporal reorganization involving multiple components of their circadian system.[3] Understanding these mechanisms offers valuable insights into enhancing human circadian adaptability, which lacks such flexibility.[33]

This remarkable flexibility is closely tied to birds' ability to synchronize their internal clocks with environmental cues, particularly photoperiodic signals. Migratory birds achieve this synchronization through multiple pathways, including deep brain photoreceptors, retinal pathways that convey light information, and the photosensitivity of the pineal gland.[4] These photoreceptive systems form part of a multi-oscillator framework that enables precise temporal coordination while maintaining the flexibility needed to adapt to environmental changes, such as shifts in day length and light intensity during migration.

This temporal flexibility is underpinned by precise transitions regulated by an autonomous circadian clock entrained to sunset cues. Laboratory studies reveal that migratory birds display consistent onset times for nocturnal activity, coinciding with local sunset, even in the absence of external temporal cues.[3,34–36] Advanced tracking technologies have further uncovered distinct activity bouts: one for daily tasks and another for migratory restlessness (Zugunruhe), with these sometimes operating on separate free-running periods.[37,38] This dual-oscillator system allows birds to maintain nocturnal activity while preserving diurnal functionality.

The precision of these transitions is evident in how birds initiate nocturnal migratory flights within specific windows relative to sunset, demonstrating temporal consistency across changing environments.[39] Unlike mammals, which rely on retinal photoreceptors for photoperiodic information, birds utilize deep brain photoreceptors to directly detect environmental light conditions and adjust their circadian rhythms accordingly.[4] This capability allows birds to rapidly adapt to challenges such as nest loss or translocation, further highlighting the robustness of their circadian system.[40]

Studies also reveal that the migratory oscillator often operates with a slightly longer free-running period (~24.8 hours), facilitating nocturnal activity essential for migration.[4,37] By integrating sensory input from deep brain photoreceptors and synchronizing their circadian clocks to environmental cues, birds achieve the precise temporal

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organization required for migratory success. This multi-oscillator system underscores the importance of circadian flexibility in supporting the complex demands of migration.

Behavioral Transitions

Advanced tracking technology has provided nuanced insights into how wild migratory birds transition between diurnal and nocturnal activity patterns. For instance, accelerometry and multi-sensor data loggers reveal that species like the Tawny Pipit (Anthus campestris) can switch rapidly between daytime activity and nocturnal migration, maintaining this flexibility throughout their journey.[40] These transitions often coincide with specific time windows relative to sunset, underscoring the precision of their temporal organization.[39] In European blackbirds, automated radio telemetry has demonstrated that migratory individuals show no significant behavioral differences from non-migrants during the pre-migratory period, yet they abruptly switch to nocturnal activity on departure nights. Most departures occur within four hours after civil dusk, reflecting a tightly controlled temporal mechanism.[41] Similarly, Northern Wheatears initiate migration within precise departure windows, typically between civil and nautical twilight, while maintaining diurnal activity patterns until the day of departure.[42] These findings highlight the remarkable temporal plasticity in avian circadian systems, demonstrating that the transition from diurnal to nocturnal activity may occur more abruptly and flexibly than previously thought, challenging earlier laboratory-based assumptions. By integrating behavioral observations with molecular and neural investigations, researchers can explore the mechanisms enabling such rapid temporal shifts. Understanding these processes across species may inform the development of interventions to help shift workers better adapt to schedule changes.

Metabolic Control in Migratory Birds

Migratory birds demonstrate a remarkable capacity for energy regulation, particularly through the integration of hypothalamic circuits such as the mediobasal hypothalamus. This brain region plays a central role in managing metabolic demands during migration by modulating seasonal shifts in gene expression related to glucose and lipid metabolism, as well as oxidative phosphorylation.[43]

Seasonal shifts in metabolic pathways are finely tuned to meet the energy-intensive requirements of migration. For instance, black-headed buntings show significant upregulation of genes involved in oxidative phosphorylation in the hypothalamus and liver during migratory states, aligning energy production with increased physical demands.[44] Additional evidence comes from red-headed buntings, where changes in hypothalamic neuropeptide activity were linked to hyperphagia and weight gain, critical behaviors for migration. These adjustments reflect the hypothalamic system's ability to orchestrate energy storage and expenditure during seasonal transitions.[45] Similarly, European starlings display tissue-specific adaptations, with flight muscles upregulating genes for energy metabolism, while the liver exhibits only minor changes.

This highlights how migratory birds optimize energy use in tissues, which directly contributes to flight performance.[46] Further supporting this, transcriptome-wide analyses of black-headed buntings reveal significant differences in liver gene expression between migratory and non-migratory states. Genes associated with lipid metabolism and other energy pathways show clear seasonal modulation, providing insight into the molecular basis of long-distance flight.[2] Together, these studies underline the intricate, tissue-specific regulatory mechanisms that allow migratory birds to sustain their extraordinary journeys.

The mediobasal hypothalamus coordinates seasonal transitions through multiple neuroendocrine pathways. This integration involves both classical neurotransmitter systems and specialized ependymal cells called tanycytes, which respond to both metabolic and photoperiodic signals.[47] With their strategic location and nutrient-sensing capabilities, these tanycytes regulate hormonal and metabolic signals, orchestrating the seasonal physiological transitions required for migration.

Studying these precise metabolic mechanisms could inform the development of interventions targeting circadian-related metabolic disruptions, such as optimizing meal timing, improving sleep-wake cycles, or designing drugs to modulate specific hypothalamic pathways.

Proposed Research Agenda

Translating Avian Temporal Plasticity to Human Medicine

The remarkable temporal adaptations observed in migratory birds suggest innovative research directions for human chronotherapy.[3] The avian model demonstrates how biological systems can maintain multiple coordinated oscillators, providing a framework for investigating similar mechanisms in humans.[4]

Table 1 summarizes the key avian adaptations discussed in this perspective and their potential applications in human circadian medicine. These adaptations highlight the remarkable temporal plasticity of migratory birds and provide a framework for exploring innovative approaches to address circadian disruptions in humans.

This temporal organization system could be particularly relevant for developing new therapeutic approaches in several key areas:

Metabolic Synchronization

The precise metabolic control exhibited by migratory birds during their temporal transitions provides a valuable model for identifying therapeutic targets in human metabolic disorders. Birds exhibit remarkable adaptability in their metabolic regulation, which is tightly coordinated with changes in activity and energy demands during migration. Studies have shown that hypothalamic circuits in migratory birds demonstrate differential expression of genes regulating glucose and lipid metabolism during these states, allowing them to optimize energy utilization and storage for long-distance travel.[43]

In humans, circadian rhythms play a similarly critical role in regulating metabolic processes. Peripheral tissue clocks, such as those in the liver and muscles, exhibit partially autonomous circadian oscillations while remaining influenced by the central suprachiasmatic nucleus (SCN). However, misalignment between these clocks, as observed in conditions like shift work, disrupts metabolic homeostasis, leading to insulin resistance, obesity, and an increased risk of diabetes.[25,26]

Current interventions for circadian misalignment largely focus on systemic strategies, such as timed light exposure, dietary adjustments, and sleep-wake schedule optimization, to restore synchrony between central and peripheral

Table 1 Key Avian Adaptations and Their Potential Applications in Human Circadian Medicine

Avian Adaptation	Key Findings	Potential Human Applications
Temporal Flexibility	Birds transition rapidly between diurnal and nocturnal activity patterns during migration with precise timing relative to sunset	Biomarker-guided chronotherapy for shift workers; Optimization of light exposure timing for circadian disorders
Multi-oscillator System	Birds maintain multiple coordinated oscillators involving pineal gland, retina, and hypothalamic structures	Development of targeted interventions for peripheral oscillators; Personalized approaches based on individual chronotypes
Metabolic Control	Hypothalamic circuits show seasonal shifts in gene expression related to glucose and lipid metabolism during migratory states	Chronotherapeutic approaches for metabolic disorders; Optimized meal timing strategies for circadian alignment
Unihemispheric Sleep	Birds exhibit true unihemispheric slow-wave sleep, particularly during migration1	Exploration of hemispheric asymmetry in human sleep; Development of strategies to enhance sleep quality in challenging environments
Environmental Cue Integration	Birds synchronize internal clocks using multiple zeitgebers (light, temperature, feeding)	Sequential timing of environmental cues for enhanced circadian entrainment; Temperature-based interventions for circadian disruption
Neural Plasticity	Birds demonstrate remarkable neural plasticity in hypothalamic circuits during seasonal transitions	Circuit-specific interventions using non-invasive techniques like TMS; Neuroimaging-guided approaches to enhance circadian adaptability
Light Sensitivity	Birds possess extra-retinal photoreceptors and show pronounced entrainment to light	Optimization of light therapy parameters; Development of targeted phototherapeutic approaches

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oscillators. For example, time-restricted eating has shown promise in aligning liver metabolic rhythms with behavioral activity cycles. However, these approaches do not directly manipulate specific peripheral clocks.[26] Advances in molecular biology, including CRISPR gene-editing techniques and the development of small-molecule modulators of circadian proteins, hold promise as tools for achieving tissue-specific circadian modulation.[48] For instance, CRISPR enables precise editing of genes involved in circadian regulation, providing opportunities to study and potentially correct disruptions in specific tissues. Similarly, compounds targeting circadian regulators, such as REV-ERB agonists, are being investigated in preclinical studies for their ability to modulate the timing of cellular processes, including glucose metabolism and lipid synthesis, with potential therapeutic applications.[25]

Despite these advances, the ability to independently manipulate peripheral oscillators without disrupting other systems remains underexplored. Peripheral oscillators, such as those in the liver, are critical for regulating metabolic processes and maintaining systemic circadian synchrony. For example, resetting the circadian rhythm of the liver while maintaining the synchrony of other peripheral clocks is a theoretical possibility but has not yet been demonstrated in clinical practice.[49,50] Addressing this gap could pave the way for highly targeted therapies for metabolic disorders, particularly for populations with circadian rhythm disruptions, such as shift workers or individuals with diabetes. However, further research is needed to develop precise tools for manipulating peripheral clocks in a coordinated manner to avoid unintended disruptions in overall circadian harmony.

Future research should prioritize understanding the mechanisms through which peripheral tissue oscillators are regulated and develop methods to modulate them independently. By leveraging insights from avian models, which showcase the ability of decentralized clocks to maintain precise metabolic control, it may be possible to design novel chronotherapeutic approaches that directly target peripheral tissues. Such strategies hold promise for mitigating the metabolic consequences of circadian misalignment and improving overall metabolic health in humans.

Sleep Architecture and Plasticity

Migratory birds display exceptional neural plasticity, enabling rapid adaptation to changing temporal demands. This plasticity, particularly in hypothalamic circuits regulating sleep-wake transitions, involves complex interactions between multiple oscillator systems and activity-dependent neural modifications.[1,28] Insights from avian models suggest a few research hypotheses for enhancing human circadian adaptability:

Circuit-Specific Interventions

Mediobasal hypothalamic circuits exhibit significant plasticity and play a central role in the temporal adaptations required for migration. These regions integrate photoperiodic and metabolic cues, providing a foundation for future research exploring non-invasive interventions to modulate these circuits and improve circadian adaptability.[4,51] Inspired by avian temporal flexibility, non-invasive approaches such as transcranial magnetic stimulation (TMS) offer therapeutic opportunities for targeting sleep regulatory circuits in humans.

Transcranial Magnetic Stimulation (TMS)

Migratory birds exhibit remarkable adaptability in their circadian systems, with rapid neural plasticity and coordination between oscillator systems during migratory periods[1.] Similarly, TMS has been shown to modulate human brain circuits involved in sleep-wake transitions. While key sleep-regulatory regions like the dorsomedial hypothalamus (DMH and ventrolateral preoptic nucleus (VLPO) lie deep within the brain and cannot be directly targeted by TMS, the technique can influence these circuits indirectly by modulating functionally connected cortical regions.[52] Emerging evidence also supports the application of TMS in primary sleep disorders, such as insomnia and hypersomnia, where modulation of cortical excitability has shown potential therapeutic effects.[52] In particular, repetitive TMS (rTMS) targeting the prefrontal cortex has demonstrated improvements in sleep quality and daytime functioning, as highlighted in recent clinical trials.

Building on insights from avian temporal flexibility, TMS research has revealed important therapeutic opportunities for modulating human sleep regulation. Recent evidence shows that TMS can independently influence both sleep architecture and mood regulation through effects on cortical-subcortical networks.[53] Specifically, TMS can enhance neuroplasticity, modify cortical excitability, and improve functional connectivity between brain regions involved in sleep

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regulation. For example, TMS has been shown to improve sleep quality independent of its antidepressant properties, suggesting direct effects on sleep circuits.[53] These findings support the potential for TMS to be a promising avenue for developing targeted interventions to enhance human circadian adaptability.

Behavioral and Environmental Modulation Inspired by Avian Models

Migratory birds exhibit remarkable temporal plasticity, adapting their circadian systems to environmental cues, such as transitioning from diurnal to nocturnal activity during migration.[40] Recent evidence demonstrates that individual birds show consistent responses to temperature cues when timing their migration departure, suggesting a precise mechanism for environmental synchronization.[54]

Inspired by these adaptations, sequentially timed zeitgebers, such as light exposure followed by feeding, may enhance human circadian re-entrainment more effectively than simultaneous stimuli.[3] Additionally, ambient temperature, an underexplored zeitgeber in human studies, plays a significant role in avian and mammalian circadian regulation, as shown in both migratory birds and mammals.[4,55]

Emerging research highlights how individual variability in circadian precision—a trait observed in avian species—can guide the development of personalized interventions for humans based on chronotype, light sensitivity, and response to temperature fluctuations.[56] Investigating whether such tailored interventions improve the resilience of human circadian systems under modern lifestyle challenges, such as irregular work hours, could bridge avian and human research effectively.

These avian-inspired approaches underscore the importance of exploring synergistic effects among various zeitgebers to better understand circadian plasticity and develop innovative strategies for mitigating circadian disruptions in humans.

Novel Approaches to Human Circadian Entrainment

Drawing inspiration from the precise temporal coordination seen in migratory birds, novel strategies to enhance human circadian entrainment can be developed. The ability of birds to synchronize multiple environmental cues, such as light, feeding, and activity, offers a model for mitigating the circadian challenges faced by humans, such as shift work and jet lag. The following research directions build on these insights:

Temporal Sequencing of Environmental Cues

Migratory birds exhibit remarkable precision in coordinating internal clocks with external zeitgebers, particularly during migration. Building on this, research should explore whether specific sequences of environmental cues are more effective for circadian entrainment than their simultaneous presentation. For example, the timing of light exposure relative to feeding and activity may significantly influence circadian adaptation in humans. Studies on synergistic interactions between zeitgebers suggest that properly timed exposure to multiple cues can strengthen diurnal rhythms and reduce the detrimental effects of circadian disruption.[3,57]

The synergy between multiple zeitgebers, such as light, feeding, temperature, and exercise, a hallmark of avian circadian adaptability, offers valuable lessons for human applications. Future studies should investigate how these environmental cues can be coordinated to enhance adaptation to circadian challenges. Particular attention should be given to individual variations, including differences in light sensitivity and intrinsic circadian periods, as these factors influence how humans respond to environmental synchronization.[58]

Properly sequencing these cues could improve therapeutic strategies for addressing circadian misalignment, such as those faced by shift workers or individuals with jet lag. For example, applying light exposure at specific intervals relative to meals and activity may optimize the alignment of circadian rhythms. These insights underscore the need to design personalized, evidence-based protocols for humans inspired by the robust entrainment mechanisms observed in birds.

Exercise-Based Circadian Modulation

Exercise has been identified as a potent zeitgeber that can complement other environmental cues. Evidence from human studies indicates that properly timed physical activity may enhance circadian adaptation, similar to how birds adjust activity patterns in response to environmental demands. Future research could investigate the optimal timing of exercise relative to other cues, such as light exposure or feeding schedules, to maximize therapeutic potential.[59] Individual variations in circadian timing should also be considered to personalize exercise-based interventions.

Biomarker-Guided Timing

Migratory birds provide a compelling model for understanding circadian adaptability, as they rely on complex temporal organization during long-distance flights. These birds integrate multiple environmental and physiological cues, such as light, temperature, and energy reserves, to optimize timing for behaviors like nocturnal migration and stopover feeding.[3,4] Inspired by this multifactorial strategy, human research could explore protocols that combine multiple validated biomarkers—such as melatonin levels, core body temperature, and activity patterns—to more accurately guide intervention timing. This approach could advance chronotherapy interventions by mimicking the birds' ability to synchronize diverse inputs for optimal performance, improving alignment between internal clocks and external demands.

This biomarker-guided framework may hold particular promise for addressing diseases linked to circadian misalignment, such as metabolic disorders and sleep disturbances. Additionally, integrating multiple biomarkers into personalized intervention strategies reflects the dynamic and interconnected nature of human circadian systems, drawing directly from the flexibility observed in migratory birds. These avian-inspired insights could inform the development of therapies tailored to individual chronotypes and specific environmental challenges.[3,4,60]

Recent advances in continuous physiological monitoring make this multi-biomarker approach increasingly feasible, allowing for real-time tracking of circadian phase markers to guide intervention timing.

Neuroimaging-Guided Research

Migratory birds demonstrate remarkable temporal flexibility, synchronizing internal clocks with external environmental cues to achieve precise behavioral transitions during seasonal migrations. These adaptations offer a valuable framework for exploring strategies to mitigate circadian disruption and improve temporal organization in humans.

While migratory birds demonstrate robust multi-oscillator systems facilitating precise temporal adaptability, the connection to human neuroplasticity and circadian adaptations remains largely speculative and underexplored. Testing these parallels in humans presents an exciting avenue for future research, particularly through neuroimaging studies that map network-level dynamics.

Building on this, advances in functional MRI (fMRI) techniques provide the ability to map dynamic changes in human neural networks during transitions between wake and sleep, revealing insights into temporal flexibility. For instance, migratory birds adjust specific hypothalamic circuits to regulate circadian plasticity. Similarly, fMRI studies have shown circadian-driven changes in functional connectivity, offering parallels to the multi-oscillator systems observed in birds.[61] Moreover, BOLD oscillations during transitions between wake and sleep have been shown to reflect dynamic neural network changes modulated by circadian rhythms, further supporting this connection.[62,63]

Existing human studies using neuroimaging have revealed circadian influences on functional connectivity and brain activity patterns.[62] Expanding this evidence base to include neural correlates of circadian disruption could help bridge avian-inspired models to human translational research by identifying how neural networks adjust under these disruptions. Despite current imaging limitations in studying small hypothalamic structures like the dorsomedial hypothalamus (DMH) and ventrolateral preoptic nucleus (VLPO)—key regions for sleep and circadian regulation—newer analytical methods have identified patterns of regional homogeneity and low-frequency fluctuations reflecting circadian and homeostatic influences on brain activity.[64]

By applying neuroimaging to understand how human brain networks adjust during circadian transitions, researchers can build on lessons learned from avian models to develop innovative therapeutic strategies. Migratory birds provide an exceptional biological model for synchronizing internal systems to external cues. These insights could inform biomarker-guided interventions, personalized strategies for shift workers, and new approaches for mitigating circadian misalignment. Leveraging advanced imaging techniques inspired by avian circadian plasticity, we can better understand the temporal dynamics of human brain activity and their implications for health and well-being.

Hemispheric Asymmetry in Sleep: From Birds to Human Research

Migratory birds' unihemispheric sleep provides a model for understanding subtler forms of hemispheric asymmetry in humans. This connection informs specific research directions, including DMN vigilance, temporal dynamics, and neural mechanisms.

Recent evidence demonstrates that humans, like migratory birds, exhibit a form of hemispheric asymmetry during sleep in unfamiliar environments, though with important differences.[65] While migratory birds exhibit true unihemispheric sleep, humans display a subtler asymmetry during sleep, characterized by reduced slow-wave activity (SWA) in the left hemisphere of the default mode network (DMN)—a brain network associated with wakeful rest and introspection—and enhanced responsiveness to external stimuli.[65,66] This adaptive function parallels the night watch system in birds, although it relies on partial neural asymmetry rather than complete hemispheric independence.[67] Exploring these parallels could inspire research on human sleep adaptations in challenging contexts.

Building on This Parallel, We Propose Three Potential Key Research Areas

DMN Night Watch Function

Investigate the adaptive role of asymmetric activity in the DMN during sleep, particularly in novel environments:

Examine how the DMN maintains selective vigilance while preserving the restorative functions of sleep.

- Study whether asymmetric DMN activity functions as a protective mechanism akin to the night watch behavior in birds. This asymmetric activity appears context-dependent, with differential engagement of the DMN during tonic versus phasic REM sleep.[66] It may represent a protective adaptation that balances vigilance and restoration by maintaining arousal thresholds in novel or potentially threatening contexts. Understanding these dynamics could shed light on how humans adapt neural activity to unfamiliar environments while preserving the restorative functions of sleep. Such insights may reveal neural mechanisms that enhance sleep resilience and suggest interventions to optimize sleep quality in challenging environments.[68]

Temporal Dynamics of Asymmetry

Examine the temporal evolution and environmental modulation of hemispheric asymmetry in human sleep:

- Explore how hemispheric asymmetry evolves over time in novel environments and its implications for sleep quality and adaptation.[69]

Determine whether asymmetry persists or diminishes on non-consecutive nights within the same environment.

- Assess how asymmetry patterns relate to sleep quality measures, including restorative function and subjective sleep perception.
- Investigate how environmental factors, such as light exposure or noise, influence asymmetry during sleep, inspired by light-dependent mechanisms in avian unihemispheric sleep.[69]

Neural and Molecular Mechanisms

Identify the molecular and neural pathways underlying hemispheric asymmetry in human sleep:

- Explore differential expression of circadian regulators and neurotransmitter systems between hemispheres, inspired by avian models. While genes like BMAL2 and pathways such as TGF-β signaling are implicated in birds, their role in human sleep asymmetry warrants further investigation.[28,65–67]
- Investigate how sensory gating mechanisms modulate hemispheric asymmetry, particularly in response to auditory or visual stimuli during REM and NREM sleep. This could clarify how the brain balances vigilance and sensory suppression to optimize sleep.[66]

This research agenda emphasizes how insights from avian unihemispheric sleep can inform studies of human hemispheric asymmetry during sleep. While migratory birds exhibit robust hemispheric independence, human sleep adaptation relies on subtler forms of neural plasticity and asymmetry. By translating findings from birds to humans, researchers can explore mechanisms for improving sleep quality and adaptability in challenging environments, such as unfamiliar sleeping conditions or shift work. These insights could also inform interventions for populations facing circadian disruptions, such as shift workers or individuals with insomnia, advancing strategies to enhance vigilance, restfulness, and overall circadian health.[3,56]

Challenges and Limitations

While the avian-inspired research agenda presented in this perspective article offers promising directions for sleep and circadian medicine, we acknowledge several translational challenges. First, the neuroanatomical and physiological differences between birds and humans necessitate careful extrapolation of findings. Second, the technical feasibility of implementing some proposed approaches, such as biomarker-guided chronotherapy, requires validation through preliminary studies before clinical application. Third, ethical considerations and regulatory frameworks will influence the pace at which these innovations can be implemented in clinical settings. We propose that these challenges be addressed through interdisciplinary collaboration, pilot studies with clear translational endpoints, and ongoing dialogue between basic scientists and clinicians to ensure that promising avian-inspired concepts can be practically and effectively translated to human applications.

Conclusion

Migratory birds display extraordinary temporal adaptability, orchestrating complex physiological and behavioral mechanisms to navigate the challenges of migration. Their remarkable capacity for temporal plasticity, from maintaining synchronized circadian rhythms to employing unihemispheric sleep strategies, provides valuable insights for human sleep and circadian medicine. While the specific molecular and neural mechanisms differ between birds and humans, understanding how birds achieve precise temporal transitions could inform the development of targeted interventions for circadian disorders. Future research should focus on translating these avian insights into practical applications, particularly in addressing circadian misalignment in shift workers and optimizing sleep quality across different environments. The key will be leveraging emerging tools like neuroimaging and biomarker-guided approaches while respecting the distinct features of human circadian biology.

While parallels between avian and human circadian systems provide a robust foundation for the hypotheses proposed, several ideas remain speculative. For instance, the roles of multi-oscillator systems or molecular pathways like BMAL2 in human neuroplasticity have yet to be experimentally validated. This perspective aims to delineate these gaps as opportunities for future research, encouraging the integration of avian insights into human studies. While these proposed research directions represent theoretical possibilities rather than established pathways, such conceptual exercises are essential for advancing our understanding of human circadian biology. By drawing inspiration from avian adaptations, we aim to stimulate innovative approaches to human circadian medicine, acknowledging that not all hypotheses will prove viable but maintaining that creative exploration is crucial for field advancement.

The success of this research agenda depends critically on interdisciplinary collaboration between chronobiologists, sleep scientists, ornithologists, clinicians, and bioengineers. Such collaboration will facilitate the empirical validation of avian-inspired hypotheses through carefully designed human studies that acknowledge both the potential and limitations of cross-species translation. Ethical considerations must guide this work, particularly as we develop interventions that may alter fundamental biological rhythms. By addressing these considerations while pursuing the research directions outlined in this perspective, we can advance circadian medicine in ways that improve human health while respecting biological complexity and individual differences in circadian biology.

Data Sharing Statement

No new data was generated for this manuscript.

Author Contributions

Ahmed S. BaHammam: Conceptualization, Writing – original draft preparation, Writing – review and editing, and Supervision. The author gave final approval of the version to be published; has agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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