

Circadian Rhythms

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Circadian rhythms are daily (about 24 h) rhythms of behaviour, physiology and biochemistry that are controlled by internal clocks. These rhythms are entrained by environmental cues, and modulate cognitive performance.

INTRODUCTION

0439.001 The rotation of the earth about its axis creates daily cycles of light, temperature, humidity and other geophysical variables that have had a profound impact on the evolution of life. Most living organisms, from single-celled bacteria to fungi, plants and animals, exhibit daily rhythms in their biochemistry, physiology and behaviour that mirror the dramatic environmental changes that define the solar day. Some daily rhythms may represent a direct response to environmental stimuli, but most are controlled by one or more internal, 'circadian' clocks (from the Latin *circa*, 'about' and *dies*, 'day'). The primary function of these circadian clocks is to organize and synchronize the organism's cellular and behavioural activities with the outside world. By internalizing the mechanism for rhythmicity, the organism can anticipate and prepare in advance for predictable changes in its environment. Circadian clocks have been further exploited in some species to regulate seasonal reproductive cycles by measuring day length, and to enable certain cognitive operations that require internal representations of time of day.

0439.002 While daily rhythms in the activity of plants and animals have undoubtedly always been recognized, the existence of endogenous circadian clocks was a matter of contention until the latter half of the twentieth century. The most compelling evidence for these clocks is the observation that daily rhythms persist (free run) when organisms are maintained in environments lacking 24 h time cues, such as in a controlled laboratory, at the poles, or in orbit aboard the space shuttle. The average duration ('period') of one complete cycle under these

conditions usually deviates slightly from 24 h, hence the designation 'circadian'. The period varies both within and between species; in temporal isolation, the circadian clock of the typical mouse completes a cycle in less than a day (about 23.5 h), whereas in most humans the clock cycles at a rate slower than one solar day (the most current estimate is about 24.1 h).

Research on circadian rhythms attempts to answer the following fundamental questions. How are circadian rhythms synchronized with the environment? What are the neural and genetic mechanisms of the circadian clock? What are the consequences of circadian rhythmicity for human performance, health and welfare?

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ZEITGEBERS AND ENTRAINMENT

According to the terminology used in the study of biological clocks, a rhythm is any process that repeats itself at regular intervals. A device that produces a rhythm can be said to 'oscillate'. An oscillator can be used like an hourglass to measure the passage of time. If the oscillator is synchronized to the solar day, it can also be used as a 24 h 'clock' to recognize local time, analogous to a sundial or digital wristwatch. A circadian clock is therefore an oscillator that has a mechanism by which it is synchronized to the solar day. Without such a mechanism, the circadian clock would generate daily rhythms that would drift in and out of optimal alignment with the environment. The mechanism for synchronization is therefore vital to the adaptive function of circadian clocks.

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Circadian rhythms are strongly synchronized to 24 h light-dark (LD) cycles by a process of 'entrainment', defined as phase and period control of one oscillation by another. 'Phase' refers to any discrete point in the cycle, such as the wake-up time within the daily sleep-wake cycle. Thus, when the circadian sleep-wake rhythm is entrained to a 24 h LD

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cycle, its period is exactly 24 h, and wake-up time occurs at about the same time within each LD cycle (e.g. when the lights come on in diurnal species, and when the lights go off in nocturnal species). Any stimulus that can entrain another periodic process is a 'zeitgeber' (from the German, 'time-giver').

The mechanism of LD entrainment has been investigated by exposing animals to brief pulses of light (from seconds to hours in duration) during prolonged recordings in constant dark. Light exposure early in the 'subjective night' (that portion of the circadian cycle when the animal acts as if it were night) resets the circadian cycle back to an earlier phase (a 'delay' phase shift; Figure 1). Light exposure late in the subjective night resets the clock forward to a later phase (an 'advance' phase shift). The brighter or longer the light pulse, the larger the shift. Light exposure during most of the 'subjective day' (when the sun would normally be up) typically has little or no effect. Entrainment is accomplished by small, light-induced phase shifts at the dawn and dusk transitions that precisely compensate for the difference between the periodicity of the LD cycle (normally exactly 24 h) and that of the circadian cycle (normally about 24 h). In humans, light during the first half of the night (before the body temperature reaches its minimum, about 2–4 h before the habitual wake-up time) induces delay shifts, while light later in the night induces advance shifts.

Although the LD cycle is the dominant zeitgeber for most species, several nonphotic zeitgebers have also been identified. Daily cycles of temperature can entrain rhythms in some species, although even in plants and poikilothermic animals this does not involve a direct effect of temperature on the rate at which the clock cycles. The biochemical machinery of the circadian clock includes a mechanism for temperature compensation, such that the circadian cycle is relatively constant across a range of tissue temperatures. If this were not the case, the 'clock' of poikilotherms would serve better as a thermometer than as a timepiece.

A number of vertebrate species can be entrained by daily schedules of food intake, and some can also be entrained or phase shifted by scheduled bouts of physical exercise or nonspecific arousal. These behavioural zeitgebers appear to be most effective at times of day when the animal would normally be asleep. The circadian timekeeping system thus appears to have the flexibility to adjust daily rhythms to important nonphotic stimuli that might be of more immediate consequence to survival than is the LD cycle.

NEURAL MECHANISMS

The biological system generating circadian rhythmicity has at its core three integrated components: a self-sustaining circadian clock, an entrainment pathway by which zeitgebers can influence the clock, and one or more output pathways by which the clock confers rhythmicity to other systems (Figure 2). In mammals, the 'master' circadian clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus. The SCN receives LD information directly from the retina, via a pathway that does not participate in form vision. Damage to the SCN disrupts or eliminates circadian rhythms in all mammals so far studied. Electrical or chemical stimulation of SCN neurons can phase shift circadian rhythms. Individual SCN neurons, grown from embryonic cells in culture, oscillate with a circadian periodicity. Remarkably, transplants of embryonic SCN tissue to adult animals can rapidly restore circadian rhythmicity lost by SCN damage. These observations converge in support of a hypothesis that the SCN is the master circadian clock in mammals. This is an exceptional example of the use of complementary techniques to establish the function of a discrete brain structure.

Because of its importance for normal circadian organization of behaviour and physiology, the SCN is accorded the status of 'master' oscillator, or 'pacemaker'. However, other circadian oscillators may also exist. One example is the retina, which contains a circadian oscillator that drives daily rhythms of its own local processes, such as photoreceptor disc renewal. In birds and reptiles, the pineal gland, retina and hypothalamus may all contain circadian oscillators, although the role of these as pacemakers or secondary oscillators varies across species.

The SCN receives major inputs from several other brain structures, some of which are important for nonphotic entrainment (e.g. inputs from the thalamic intergeniculate leaflet and pontine raphe nuclei). Neurons of the SCN in turn send axons to a limited number of structures, primarily within the hypothalamus, which presumably disperse circadian timing information more widely. The SCN may also send rhythmic signals by a diffusible factor, conveyed in the extracellular fluid, cerebrospinal fluid or blood.

GENETIC MECHANISMS

Circadian rhythms are genetically programmed and, although sensitive to environmental cycles, do not require these cycles to develop normally.

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Circadian phenotypes can be selected by breeding, and can be altered by gene mutations. Genetic differences are thought to underlie variability in human rhythms, such as the 'night owl' versus 'early bird' phenotypes.

0439.013 In all species studied so far, circadian rhythms appear to be generated by an intracellular feedback loop involving a set of 'clock' genes and their protein products. Activation of these clock genes induces the synthesis of proteins, which then feed back upon and temporarily inhibit further clock gene expression. As clock proteins gradually degrade, clock genes are released from inhibition and protein production is renewed. Positive and negative regulators of clock gene expression are articulated in such a way as to produce an approximately 24 h cycle of cellular activity. Zeitgebers shift and entrain the clock by altering clock protein levels. Putative clock genes have been identified and cloned in fungi, fruit flies and mammals, and the feedback principle and some of the specific genes appear highly conserved across a range of phylogenetic groups. A complete molecular description of the circadian 'clockworks' can be expected soon for several species.

CONSEQUENCES OF CIRCADIAN RHYTHMS FOR COGNITION

0439.014 Consistent with its ubiquitous role in physiological regulation, the circadian timing system also influences performance on cognitive tasks. This is in part secondary to circadian regulation of arousal or alertness, which in LD-entrained humans is low early in the morning and peaks in the early evening, in parallel with the circadian rhythm of body temperature. Performance speed on cognitive tasks that stress simple, repetitive throughput of information, as in tests of vigilance (e.g. detection of an infrequent signal), serial search, card dealing, additions, and reaction times, follows the same circadian function, with the best scores achieved in the evening. Performance accuracy on some of these tasks varies inversely with body temperature. Tasks stressing short-term memory also generate better scores earlier in the day, before the body temperature reaches its maximum. In addition, performance on some tests of long-term memory is best when participants are tested at the same time of day at which they were trained, even when retest intervals are weeks apart. This implies that circadian time may be incorporated within the neural representations that mediate learning and recall.

The circadian clock has been adapted by many species to provide the sense of time necessary for foraging, navigating and migrating. These species can use timing information provided by the circadian clock to compensate for the movement of the sun and stars, and thereby use the position of these celestial landmarks to guide travel over great distances. Some species, including bees, fish, birds and at least some mammals, can learn and remember the time of day when food is available at specific places in the environment, without the aid of external time cues. According to one theory, circadian time may be encoded within all memories, for use in cognitive computations that guide the temporal aspects of many behaviours.

0439.016 In humans, the ability to estimate the passage of time is also regulated in part by the circadian system. In temporal isolation, subjective estimates of hourly intervals are proportional to the duration of the circadian sleep-wake cycle. Estimation of intervals in the seconds to minutes range, however, are independent of circadian time.

0439.017 Disruption of circadian rhythms, induced by transmeridian jet travel, shift-work rotation or a change in laboratory LD cycles, is associated with impaired performance on many cognitive tasks in humans and animals. Some of these effects can be attributed to the partial sleep deprivation that typically accompanies travel and shift rotation in humans, but impairments are also evident in laboratory studies that minimize sleep disruptions. Cognitive deficits that emerge across the life span may also be related to the disruptions of sleep and circadian rhythms that are a physiological hallmark of old age.

CONCLUSION

0439.018 Circadian rhythmicity is a pervasive feature of life on earth. At all levels of analysis, from molecules to behaviour, the daily cycles of the environment are reflected in the functions of the organism. The circadian clocks that have evolved to meet the challenges of the solar day modulate cognitive processes and mediate forms of animal behaviour that require precise recognition of time of day or day length.

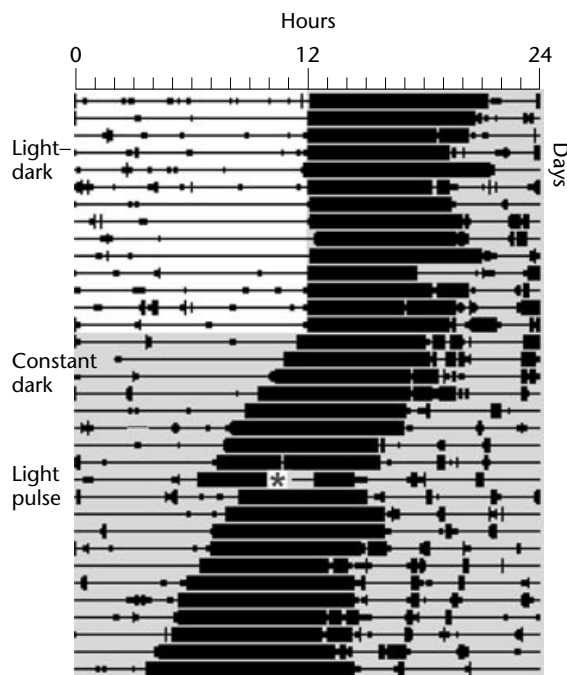
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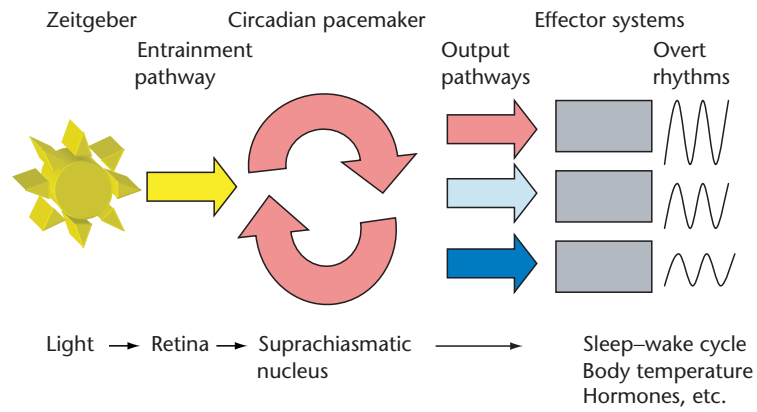
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Keywords:

zeitgeber; entrainment; phase shift; suprachiasmatic nucleus; jet lag



0439f001 **Figure 1.** Wheel-running activity of a mouse in a light-dark cycle (12 h dark period indicated by shading), and in constant darkness. Each line represents one day, plotted in 10 min time bins from left to right. Vertical deflections (heavy bars) indicate time bins when wheel running occurred. In the light-dark cycle mouse activity is nocturnal and has a periodicity of exactly 24 h. In constant dark, the activity rhythm 'free runs' with a period of less than 24 h. A 30 min light pulse (asterisk) on day 10 of constant darkness induced a 'delay' phase shift of approximately 2 h.



0439f002 **Figure 2.** Conceptual model of the core elements of the system generating circadian rhythms in mammals. Overt rhythms may vary in amplitude and phase, but when entrained to light, all exhibit the same 24 h periodicity and a relative stable phase relation with other rhythms. This defines internal temporal order.

***Encyclopedia of Cognitive Science* - author queries**

Article 439 [Mistlberger]

Further Reading

Harrington: page numbers?

Mistlberger & Rusak: page numbers?