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Biological Rhythms

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Glossary

biological rhythm Any recurrent endogenous cycle (behavioral or physiological) that persists in constant conditions in the absence of geophysical or environmental temporal cues.

circadian rhythm Endogenous rhythm that is approximately 1 day in length.

circannual rhythm Endogenous rhythm that is approximately 1 year in length.

entrainment Synchronization of an internal endogenous rhythm by a recurring external time cue such as the day–night cycle.

free running Expression of a biological rhythm in the absence of any environmental temporal cues.

photoperiod Amount of daylight in a given day; day length.

seasonal rhythm Yearly rhythm that is exogenously regulated by geophysical cues.

suprachiasmatic nucleus The primary "biological clock" located in the anterior hypothalamus of the brain that coordinates rhythmic and photoperiodic information via inputs and outputs of the nervous and endocrine systems.

A biological rhythm is any recurrent endogenous cycle (behavioral or physiological) that persists in the absence of geophysical or environmental temporal cues but is normally synchronized (entrained) with a period that approximates that of the geophysical cycle.

INTRODUCTION

As most people have experienced throughout their lifetimes, timing is everything. The ability to modify one's behavior or physiology on a regular basis, be it daily, monthly, or yearly, is arguably one of the most adaptive responses of life and occurs in virtually all organisms, ranging from single-celled algae to complex humans. But why have biological rhythms evolved, and what functions do they serve? All physiological systems require proper coordination and synchronization with one another to ensure that a wide variety of rhythmic events can occur during an optimal time of the day or year. For example, for the body to prepare appropriately to digest a meal, numerous physiological processes must occur in anticipation of eating. Many species must also predict the time of year to coordinate breeding activities. These daily and yearly changes require critical coordination among numerous internal processes necessary to maintain homeostasis. Furthermore, for biological rhythms in behavior and physiology to be coordinated with the appropriate time, these rhythms need to be synchronized to external time cues within the environment. The means by which intrinsic rhythms are generated by a clock in the brain, and how these rhythms are synchronized to local time, is the primary focus of the study of biological rhythms.

HISTORICAL OVERVIEW

The importance of coordinated timing of biological events has been known since the dawn of civilization. For example, written records dating back to Alexander the Great in the 4th century B.C. noted the daily movements of flower petals. However, the study of biological timing as an empirical science is in its relative infancy. Chronobiology, the scientific study of biological rhythms, formally began in 1729 with a brief communication by Jean Jacques d'Ortous de Mairan, who noted that the daily leaf movements of a heleotropic plant persisted in complete darkness and in the absence of any other geophysical cues. However, it was not until the 1950s, based on the pioneering work of noted "clock watchers" Colin

Pittendrigh, Serge Daan, and Jergen Aschoff, that a firm scientific understanding of the characteristics and formal properties of biological rhythms began to take shape.

TYPES OF RHYTHMS

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p0020 Since these early discoveries, a wide variety of biological rhythms have been identified in both vertebrate and invertebrate species, and these rhythms are typically categorized by the length of a single cycle. For example, circadian rhythms are daily rhythms that are approximately 24 h and mimic the geophysical cycles of day and night. The alternating pattern of activity followed by periods of rest (sleep) that are observed in most vertebrate species is the most salient example of a circadian rhythm. However, biological rhythms need not be 24 h in length. Ultradian rhythms are rhythms that occur more frequently than 24 h. For example, many hormones (e.g., cortisol) and enzymatic reactions display rhythms only a few hours in length. In contrast, infradian rhythms are rhythms longer than 24 h but shorter than 1 year. Cycles of reproductive endocrine activity, such as menstrual cycles in humans and estrous cycles in nonhuman animals, are examples of this kind of rhythm. Finally, some species display circannual rhythms, with cycle lengths of approximately 1 year that persist in the absence of environmental influences. Circannual rhythms commonly involve yearly cycles in breeding activity and reproductive endocrinology. For example, some species of birds and rodents display yearly fluctuations in gonadal mass and changes in reproductive hormones (e.g., testosterone, estrogen), and these fluctuations persist when the animals are maintained within constant conditions of the laboratory. Closely related to circannual rhythms are seasonal rhythms, which also approximate 1 year. However, unlike true circannual rhythms, seasonal rhythms are generated in response to environmental cues and do not persist in the absence of these cues.

p0025 Although many kinds of biological rhythms have been identified, the majority of research within the field of chronobiology has focused on circadian and circannual/seasonal rhythms. As will be seen later, the neuroendocrine mechanisms responsible for generating circadian rhythms are also intimately involved in generating seasonal rhythms. Because the circadian clock is necessary for seasonal rhythms, the discussion that follows outlines the means by which circadian rhythms are generated and maintained and then the mechanisms by which seasonal rhythms are generated. The article concludes with a discussion of various endocrine disorders that have been tied to abnormalities in circadian and circannual/seasonal rhythms.

CIRCADIAN RHYTHMS

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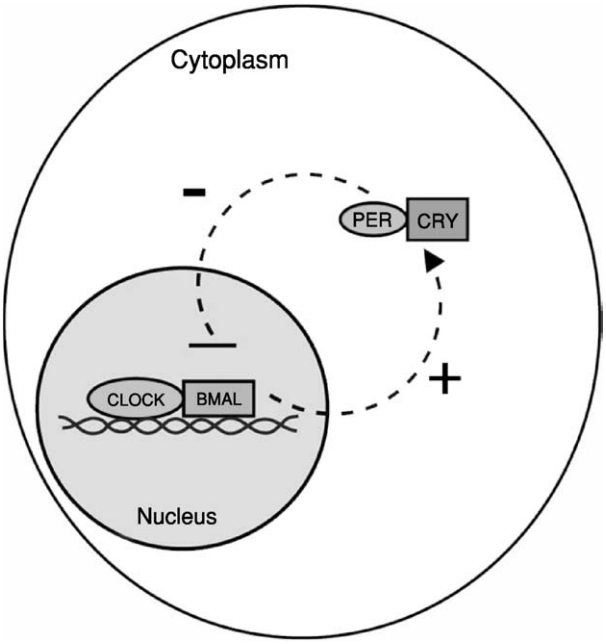
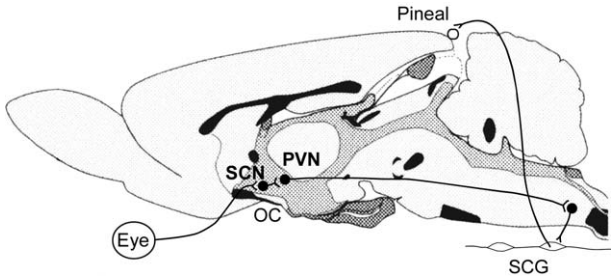
p0030 "Circadian" comes from the Latin *circa* (meaning "around") and *diem* (meaning "a day"). Virtually all measurable physiological and behavioral responses display circadian rhythms. For example, there are circadian rhythms in everything from heart rate and liver metabolism to attention and speed of decision making and reaction time. It is now known that all of these rhythms are controlled by a bilateral nucleus at the base of the brain. This brain region was identified in 1972 as an area of the hypothalamus called the suprachiasmatic nucleus (SCN). Lesions that destroy the SCN result in an abolition of all rhythmic processes from daily rhythms in hormone secretion to the sleep–wake cycle. As will be seen later, SCN lesions can also abolish seasonal rhythms.

p0035 Further evidence that the SCN is the circadian clock comes from studies showing that rhythmicity can be restored in SCN-lesioned animals by transplanting SCN tissue from a donor animal into the brains of animals with their own SCNs destroyed. This procedure restores circadian rhythms in these formerly arrhythmic animals, demonstrating that one can literally remove the circadian clock from one animal and provide it to another animal whose own clock is not functioning. Importantly, the rhythm is restored with the period of the donor, demonstrating that the restoration of circadian behavior is a property of the transplant rather than restoring function in the host animal's brain. Finally, the SCN can be removed from an animal and maintained in a culture dish, and it will continue to show circadian rhythms in neural firing rate. These studies are important because they show that circadian rhythms are contained within the SCN and are not simply being driven by temporal input to this brain region.

p0040 Knowledge of where the primary biological clock is located within the brain set the stage for investigations of the SCN at the cellular level to determine what makes the clock "tick." To draw an analogy between the SCN and a watch, if one opened the back of a watch, a large number of gears could be seen. One might know that the gears are all working together to allow the watch to function properly. However, to fully understand the watch's internal mechanism, one would have to carefully remove one gear at a time to see how it is connected to the next gear, and so on,



f0005 **Figure 1** Basic molecular model of the intracellular circadian feedback loop. The process begins in the cell nucleus when the CLOCK and BMAL proteins dimerize to drive the transcription of the *per* and *cry* genes. In turn, *per* and *cry* are translocated to the cytoplasm and translated into their respective proteins. Throughout the day, the PER and CRY proteins build within the cell cytoplasm. When levels of PER and CRY reach a threshold, they form a heterodimer, feed back to the cell nucleus, and negatively regulate CLOCK:BMAL-mediated transcription of their own genes. This feedback loop takes approximately 24 h, thereby leading to an intracellular circadian rhythm.

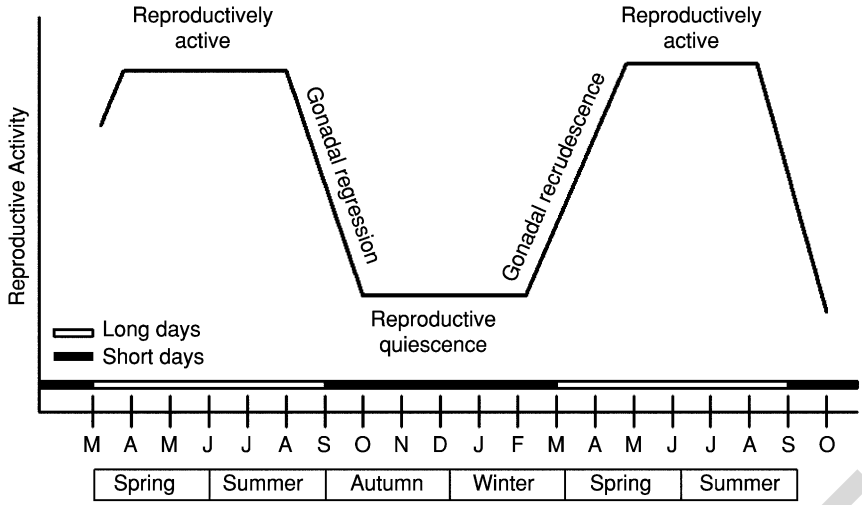


f0010 **Figure 2** Neural pathway by which environmental light reaches the suprachiasmatic nucleus (SCN) and pineal gland to regulate circadian entrainment and regulation of melatonin secretion. Light enters the retina and is transmitted to the SCN. The SCN then reaches the pineal through a multisynaptic pathway, first synapsing in the paraventricular nucleus of the hypothalamus (PVN). From here, fibers proceed through the medial forebrain bundle to the spinal cord. At this point, fibers actually exit the central nervous system and synapse onto the superior cervical ganglion (SCG) or the sympathetic nervous system. From here, sympathetic nerve fibers terminate in the pineal, where they regulate melatonin secretion. AU:1

until all of the gears were taken out. In much the same way, one can study individual cells within the SCN to see how all of the cells (approximately 10,000) in a unilateral SCN work together to keep time. Unlike the gears of a watch, individual cells within the SCN are capable of showing their own independent circadian rhythms. When one begins to look at other cells, one can see that they too show rhythms, but each cell has its own intrinsic period. So, like the question of how all of the gears of a watch work together to keep accurate time, one question of interest to circadian biologists is how all the cells of the SCN work together to produce a rhythm of 24 h.

p0045 The knowledge that individual cells of the SCN can produce a rhythm on their own suggested that the complete machinery for producing a rhythm is contained within each cell of the SCN. This information allowed researchers to begin investigating the cellular mechanisms responsible for rhythm generation. Over the past 10 years or so, enormous progress has been made uncovering the cellular and molecular mechanisms responsible for the generation of circadian rhythms within a cell. It is now known that these rhythms are produced by a feedback loop within the cell that takes approximately 24 h. The process begins in the cell's nucleus when two proteins called CLOCK and BMAL bind to one another and drive the transcription of messenger RNA (mRNA) of two genes called *period* (*per*) and *cryptochrome* (*cry*). The mRNA for these genes then migrates to the cytoplasm of the cell and is translated into PER and CRY proteins. Over the course of the day, these proteins build up within the cytoplasm, and when they reach high enough levels, they bind to one another (PER:CRY). These newly formed PER:CRY "dimers" then feed back to the nucleus, where they bind to the CLOCK:BMAL protein complex to turn off their own production. Although numerous other clock genes and their protein products have been identified, this regulatory loop provides the core molecular clock mechanism in mammals (Fig. 1).

p0050 Interestingly, over the past several years, the same clock genes (e.g., *clock*, *bmal*, *per*, *cry*) that are found in cells of the SCN have been identified in other brain areas as well as in many other peripheral tissues in the body. However, these "clocks" in other parts of the body are different from those found in the SCN. If these clocks are removed from the body, their endogenous rhythms will cycle for only a few days before dampening, whereas those present in the SCN will continue to cycle indefinitely. These findings suggest that the SCN is the master clock that is required to communicate with other subordinate



f0015 **Figure 3** Typical pattern of seasonal/photoperiodic changes in reproductive physiology in a long-day breeding rodent. Reproductive activity is maximal during the long days of summer, but reproductive regression occurs as the days get shorter during the autumn. The reproductive system maintains a period of quiescence (inactivity) during the short days of winter. As the day length increases during the spring, reproductive activation (recrudescence) occurs anew.

clocks so that they can continue to keep time. There are many reasons why these subordinate clocks might be needed in tissues other than the SCN. These clocks may be necessary for tissues to anticipate upstream signals stimulating production of specific factors. For example, the cellular machinery necessary to produce a hormone in response to stimulation could require hours of preparation within the cell. However, if the tissue has its own clock, it can turn on this machinery in advance of stimulation and be prepared to produce the hormone much faster.

p0055 The preceding findings summarize what is known about the physiological functioning of the SCN. However, for a clock to be adaptive for an organism, the clock needs to coordinate all of these rhythms with local time in the environment. In mammals, this synchronization is accomplished via a direct projection, the retinohypothalamic tract (RHT), from the eye to the SCN (Fig. 2). Unlike rod and cone photoreceptors in the retina that are responsible for black/white and color vision, respectively, the photoreceptors that communicate with the SCN are ganglion cells that are directly responsive to light because they contain a photopigment called melanopsin. Essentially, these melanopsin-containing ganglion cells project to the SCN to inform the SCN of the time in the environment. Because the SCN is synchronized (entrained) to local time, it can prepare the brain and body well in advance of the time that rhythmic processes need to occur. For example, the SCN can stimulate the pancreas to produce insulin before one eats lunch. In this way, one's body can be prepared to digest the food before one even eats.

p0060 Now that the intrinsic rhythm within the SCN is synchronized to local time, this "time-stamped" rhythmic information needs to be communicated all over the brain and body to coordinate the timing of thousands of physiological and biochemical processes. For example, the SCN needs to communicate with brain areas involved in sleep to coordinate sleep with nighttime. The SCN accomplishes this communication using both neural and humoral signals. Researchers can determine neural communication from the SCN relatively easily by using chemicals to trace the "wiring" from the SCN to its targets. Through the use of tracing techniques, it is now known that the SCN communicates neurally to a vast of array of brain targets as well as to targets in the periphery such as the liver and heart. It is also known that the SCN regulates some rhythmic functions through humoral signals. For example, if the fibers exiting the SCN in an animal are surgically cut, some circadian rhythms persist. However, because diffusible signals can essentially travel anywhere in the brain and body, the means by which these neurochemicals communicate is much more difficult to investigate experimentally. To date, two neurochemicals found in neurons of the SCN, transforming growth factor-α (TGF-α) and prokineticin-2, have been implicated as diffusible factors that may be used by the SCN to control locomotor behavior in

rodents. However, determining where specifically in the brain these chemicals act to regulate locomotor behavior requires further investigation.

s0025 CIRCANNUAL/SEASONAL RHYTHMS

p0065 Just as animals experience large fluctuations in physiology and behavior throughout a single day, many organisms experience pronounced changes across the seasons of the year. Recall that circannual rhythms are endogenously driven rhythms that approximate 1 year. Such rhythms have been demonstrated in several birds and a few mammalian species (e.g., ground squirrels, sheep). In contrast to true circannual rhythms, the majority of species display seasonal rhythms in behavior and physiology in response to predictable changes in the environment such as day length. Although seasonal rhythms are not endogenously regulated, they still produce pronounced changes in physiology and behavior throughout the year. Much of the research conducted in the area of seasonality has focused on seasonal changes in breeding and reproductive endocrinology.

p0070 Many animals are faced with potentially large seasonal fluctuations in environmental conditions, including changes in day length, ambient temperature, rainfall, humidity, food availability, and social interactions. These potentially large fluctuations can dramatically affect the world in which an animal lives. For many animals, the energy required for thermoregulation is high during the winter, a time when energy availability is typically low. Because of this "energetic bottleneck," many animals have evolved specific physiological and behavioral adaptations to cope with winter conditions. For example, some animals may migrate or reduce activity (e.g., hibernate, enter torpor) when food availability is low and energetic demands are high. Other animals restrict breeding to specific periods of the year (e.g., April–August) (Fig. 3) because breeding at inappropriate times can potentially compromise the survival of both the parents and their offspring. But how does an animal determine the optimal time of year?

p0075 As discussed previously, a wide variety of proximate environmental factors can be used in the timing of seasonal breeding, and all of these factors fluctuate seasonally. However, the majority of scientific studies suggest that animals rely mainly on day length as a primary cue with which to estimate the time of year. Most environmental cues other than day length vary in relatively unpredictable ways throughout the year. For example, although winter is usually associated with lower ambient temperatures compared with summer in the Northern Hemisphere, an unseasonably warm "Indian summer" may occur during the autumn/winter or a cold wave may roll through during the summer. Furthermore, food and water may be available to animals only sporadically throughout the year. In contrast to these seasonal factors, day length information is relatively "noise free" and can be used to coordinate energetically expensive activities (e.g., breeding) to coincide with adequate energy availability. By relying on just two pieces of information, the absolute period of daylight and the direction of change across time, animals can determine the precise time of year. For many species, breeding occurs during the long days of summer, whereas short "winter-like" days result in complete regression of the reproductive system as well as in changes in body weight and fur thickness. Interestingly, some species (e.g., sheep) actually breed during the winter. As would be predicted, the effects of day length on reproductive physiology and behavior are generally reversed in these species because their lengthy gestation time allows for birth during summer. The ability of an animal to use seasonal changes in day length to coordinate physiological and behavioral adaptations is commonly referred to photoperiodic time measurement (PTM).

p0080 How is day length information interpreted physiologically in mammals? As with circadian rhythms, seasonal changes in day length are detected by the photosensitive retinal ganglion cells within the eye that send projections to the SCN (Fig. 2), suggesting that seasonal rhythms are regulated to some extent by the circadian system. In fact, abnormalities within the circadian system that "speed up" the circadian clock also appear to accelerate the rates of seasonal responses. The SCN projects multisynpatically to the pineal gland, where the photoperiodic signal is transduced into an endocrine message. Specifically, neural activation of the pineal gland results in the production of the indolamine hormone melatonin. During prolonged periods of darkness (e.g., night), melatonin is synthesized and secreted in abundance, whereas exposure to daylight will immediately suppress the nocturnal synthesis of melatonin. The resulting rhythmic secretion of melatonin, which is intimately tuned to the presence or absence of environmental light, appears to provide the biochemical "signal" for photoperiod in mammals. In other words, the long nights and short days characteristic of winter enable the pineal gland to synthesize melatonin for a longer duration than that which occurs during the short nights and long days of summer. The increased duration of melatonin release during short days, as compared with

long days (i.e., winter vs summer), is responsible for inducing many seasonal changes, including gonadal regression and the cessation of breeding activities. Interestingly, surgical removal of the pineal gland (which removes the endogenous source of melatonin) prevents photoperiodic responses in nearly all mammalian species studied to date. Furthermore, it is the duration of the nocturnal melatonin secretion, and not the total amount of melatonin, that appears to provide important photoperiodic information, with longer durations (e.g., >12 h) associated with short days (i.e., winter) and shorter durations (e.g., <8 h) associated with long days (i.e., summer).

p0085 On secretion by the pineal during nighttime, melatonin travels to target tissues via the bloodstream, where it can bind to specific receptors located in either the brain or the periphery. Three types of melatonin receptors have been identified: Mel_{1a}, Mel_{1b}, and Mel_{1c}. Mel_{1a} and Mel_{1b} receptors have been identified in a wide range of species, whereas the Mel_{1c} receptor occurs exclusively in invertebrates. Furthermore, melatonin receptors have been identified in a wide variety of brain sites, including the SCN of the hypothalamus, the thalamus, and the pars tuberalis, a structure within the pituitary gland that is involved in regulating endocrine responses, suggesting that these brain sites may be important targets for the actions of melatonin. In addition, melatonin receptors have been isolated in several peripheral tissues, including the spleen, gonads, and adipose tissue.

p0090 The modulation of seasonal responses involves the effect of melatonin on brain mechanisms regulating peripheral responses as well as more direct actions of the hormone on organs and glands in the periphery. For example, in the context of seasonal breeding in rodents, melatonin can act on the hypothalamus to regulate the release of gonadotropin-releasing hormone (GnRH), a critical hormone in the endocrine axis regulating reproductive physiology and behavior. Thus, during short winter-like days, prolonged melatonin secretion can exert a negative influence on GnRH, resulting in reduced secretion of the reproductive hormones luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. Decreases in LH and FSH, in turn, act at the level of the gonads (e.g., testes, ovaries) to decrease sex steroid hormones (e.g., testosterone, estrogen). Reductions in these hormones lead to regression of the reproductive system and cessation of reproductive behavior, typical of winter. As the days grow longer as spring approaches, the duration of melatonin release is reduced. This removes the inhibitory influence of this hormone on the reproductive endocrine axis, and reproductive physiology and behavior are restored.

CLINICAL SIGNIFICANCE OF BIOLOGICAL RHYTHMS

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p0095 As mentioned previously, circadian and seasonal rhythms are critical for organisms to survive in a changing environment. To maintain homeostasis, hundreds of physiological and biochemical processes need to be coordinated temporally with both the environment and relative to one another within the body. As a result, normal behavioral, physiological, and psychological functioning is dependent on the body's timing systems.

p0100 For example, one particular type of clinical depressive disorder, seasonal affective disorder (SAD), is of particular interest to chronobiologists. SAD is a cyclic illness characterized by recurrent episodes of winter depression alternating with periods of normal affect during the summer. Because of the seasonal component of SAD, it has been suggested that the shortened day lengths of winter may be part of the etiology of this disorder. In fact, exposure to bright lights during early morning or early evening results in marked improvements in clinical symptoms of SAD; therefore, bright light phototherapy has become the treatment of choice for SAD. Although the precise causes of SAD are still not known, abnormal phase shifts in one's circadian rhythms and abnormal patterns of melatonin secretion both have been suggested. Phototherapy may act to shorten the duration of melatonin secretion by suppressing its production early in the morning. Alternatively, phototherapy may act to change the phase of circadian rhythms in numerous physiological factors that may contribute to this seasonal depression.

p0105 In addition to seasonal changes in mood, many organisms, including humans, display pronounced seasonal fluctuations in disease and death. Although some of these are due to seasonal changes in the pathogen (e.g., viruses, bacteria), there are also potentially large fluctuations in one's immune system. These changes in immunity likely contribute to the seasonal fluctuations in disease, although researchers are just beginning to understand the physiological mechanisms underlying these changes. As with other seasonal adjustments, seasonal changes in immunity are regulated by changes in day length. As animals use the photoperiod to time changes in reproduction, this same signal can be used to organize the timing of

immune alterations throughout the seasons. Because most human societies use artificial lighting yet still experience seasonal changes in disease and death, the mechanisms regulating seasonal changes in human immune function are likely different and require further study.

See Also the Following Articles

Circadian Rhythms: Hormonal Facets(0293) • Circadian Rhythms, HPA Axis and*(0294) • Melatonin(0858) • Pineal Gland(1018) • Sleep, HPA Axis and*(1206) • Sleep, Neuroendocrine Regulation and*(1207) • Suprachiasmatic Nucleus (SCN)*(1242)

Further Reading

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