

# Collaborative Research Feature

## A Brief Biology of Time

Photoperiod, or the length of day, has a profound impact on the complex social behaviors supporting reproduction and, more surprisingly, the functioning of the immune system.

**T**hanks to automatic alerts from the national weather service, our Google calendars, iPhones, and Blackberries, we always know the time: the minute, the hour, the day, the month, the year. We know when to buy that down jacket to insulate ourselves against the brutal Chicago winter, and we know when to think about installing our air conditioners. In many ways, our seasonal anticipatory behaviors have been conveniently outsourced.

Although modern technology has provided us with such conveniences, we remain deeply biologically tied to seasonal shifts. For example, why are we more likely to get sick in the winter when the pathogens causing our illnesses are around all year long? Why do some of us experience shifts in mood as the seasons change? Though we may live and reproduce relatively independently of the seasons, recent studies on the reproductive and immune systems of animals suggest that we may have vastly underestimated the impact of the seasonal biological clocks on our own physiology and behavior.

Our bodies know the date apart from calendars, watches, or even the weather. “We know the time of year by the length of the night - not the day. Most people guess ‘day length’ and perhaps that’s because we’re day-active mammals, but in fact the hormone that keeps track of time in all vertebrates, called melatonin, is secreted at night,” explained Brian Prendergast, Associate Professor of Psychology at the University of Chicago.

Prendergast’s research has long focused on biological rhythms, or “why we do certain things at certain times.” For many species that breed seasonally, timing is everything since they need to make sure that they reproduce

when conditions favor the survival of their young. For this reason, the bodies of many mammals have developed the capacity of closely monitoring the duration of nightly melatonin secretion into their bloodstream in order to exactly coordinate the emergence of appropriate mating behaviors at the correct time of year.

Mammals, however, engage in a host of energetically costly physiological changes that correspond with season, including growing more hair and gearing up their immune systems for difficult winter conditions. In fact, the immune system and the reproductive system display the same dependence on “photoperiod” or length of night, and these two systems interact.

“In the context of biological rhythms, immune and reproductive systems interact because they are both energetically costly processes,” Prendergast explained. Indeed, Prendergast found this to be the case even in animals that do not breed seasonally.

These seasonal fluctuations of the immune and reproductive systems influence other intricate physiological processes. The Prendergast lab is investigating the relationship between these systems in animals (especially in Siberian hamsters), the way they respond to photoperiod, and what consequences their activity has on emotional and social behaviors.

Here we survey some of the lab’s major lines of research:

### *How does length of day regulate reproduction?*

In their investigations on reproduction regulation, the Prendergast lab uses Siberian hamsters as the animal model. In the winter, the reproductive systems of Siberian hamsters shut down. By midwinter, the reproductive system starts to regenerate, a process that



takes several months, in order to be prepared for the spring. This process is controlled by whether the animal is in a “short-day” period (less than 12 hr/day) or a “long-day” period (greater than 14 hr/day)”. However, the fact that hamsters are able to begin regeneration of their reproductive systems several months before receiving the direct sunlight signal, suggests that the hamsters have some type of genetically controlled seasonal “memory”.

Working with his post-doctoral advisor Randy Nelson (The Ohio State University) in 2002, Prendergast discovered three genes critical for the functioning of seasonal clocks. These genes regulate the levels of thyroid hormone in the hypothalamus, which ultimately controls the hamster reproduction cycle.

While the precession of the planets causes quite predictable variability in the length of day and night over the course of the year, we all know that some winters are worse, and even longer, than others. How can animals account for that?

In a publication that came out earlier this year, Dr. Prendergast and colleagues Matthew Paul, Jerome Galang, and William Schwartz, discovered that hamsters are in fact, sensitive to “nonphotic cues” during the intermediate

duration photoperiods that characterize the spring and autumn. These cues could include food availability, humidity and temperature. They found that the hamsters were not at all responsive to these cues when exposed to long, summer-like photoperiods (16 hr of light/day), but when such unfavorable conditions existed in intermediate photoperiods, the reproductive systems of the hamsters failed to fully develop. This suggests that animals have a mechanism for modulating their genetically programmed light-sensitive seasonal clocks to account for seasonal variability in other environmental cues.

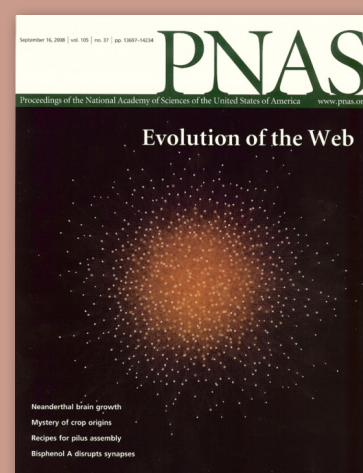
### *The immune and reproductive systems make a trade*

Siberian hamsters also show seasonal changes in their immune systems. For example, during “short-day” periods (winter months), hamsters increase their T- and B-lymphocyte numbers in circulation and enhance a number of specific lymphocyte functions. This evolutionary trait equips the immune system to deal with winter stressors and to aid in the survival of its species. Energy that was invested in reproduction over the summer gets redirected to the immune system for the time that reproduction is not feasible. Similarly, during the summer months

## IN THE CONTEXT OF BIOLOGICAL RHYTHMS, IMMUNE AND REPRODUCTIVE SYSTEMS INTERACT BECAUSE THEY ARE BOTH ENERGETICALLY COSTLY PROCESSES.

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### FEATURED PUBLICATION FROM THE PRENDERGAST LAB



**Pyter LM, Pineros V, Galang JA, McClintock MK, Prendergast BJ. (2009)** Peripheral tumors induce depressive-like behaviors and cytokine production and alter hypothalamic-pituitary-adrenal axis regulation. *Proc. Natl. Acad. Sci.*; 106(22):9069-74.

A strong and positive correlation exists between chronic disease and affective disorders, but the biological mechanisms underlying this relationship are not known. Here we show that rats with mammary cancer exhibit depression- and anxiety-like behaviors in the absence of overt sickness behaviors. The production of proinflammatory cytokines, known to induce depressive-like behaviors, was elevated in the periphery and in the hippocampus of rats with tumors compared with controls. In tumor-bearing rats, circulating corticosterone, which inhibits cytokine signaling, was suppressed following a stressor, and gene expression of hippocampal glucocorticoid receptors was elevated. The results establish that tumors alone are sufficient to trigger changes in emotional behaviors. Dampened glucocorticoid responses to stressors may exacerbate the deleterious effects of tumor-induced cytokines on affective states.

## I AM INTERESTED IN HOW OUR BODIES DECODE MELATONIN SIGNALS: DO THE IMMUNE AND REPRODUCTIVE SYSTEMS “LISTEN” TO THE SIGNAL IN THE SAME WAY?

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when reproductive activities are in full swing, the immune system is relatively weaker.

The energetic tradeoff between the immune and reproductive systems constitutes what Randy Nelson and Gregory Demas call “the winter immunoenhancement hypothesis”.

Even “sickness behaviors” (e.g. fever, anorexia, lethargy) triggered by the innate immune response (that is, first response of the immune system that is not specific to the pathogen) have been found to vary in their intensity between “short-day” and “long-day” periods, presumably to save energy.

However, Prendergast and Scott Baillie, a 2007 alumnus of the University of Chicago Psychology Department, recently noted that “bacterial infections are more common among fish during the summer, whereas viral infections peak during the winter,” which begs the question as to how mammals fend off summer infections with their relatively weaker immune systems.

Previous research on the relationship between the immune response and photoperiod had used the same type of pathogen, leading Prendergast to wonder whether the hypothesis that had been supported was just an artifact of an overly narrow experimental condition. If the “winter immunoenhancement hypothesis” could be generalized beyond just one type of infection, organisms could enhance their immune responses during winter, irrespective of whether specific pathogens were more prevalent at that time of year.

While the results of their recent study supported the “winter immunoenhancement hypothesis” over a pathogen-specific immune response model, this was the first study to look at the behavioral responses to more than one type of pathogen as a function of photoperiod. They found that the initial response of the hamsters

to both gram-negative and viral infections (termed “acute phase response”) entailed “anhedonia” or loss of pleasure-associated behaviors. In contrast, the initial response to gram-positive infection involved behavioral changes in regulation of temperature. These findings hint once again at a potential link between the way animal behavior is controlled through linked mechanisms of the immune and reproductive systems.

“We continue to be interested in the neuroimmunological mechanisms by which photoperiod regulates behavioral responses to infection,” said Prendergast.

### Photoperiod and mood

“Hamsters get ‘depressed’ over the winter,” remarked Prendergast. He found evidence to support this conclusion from a study conducted in 2005 with Randy Nelson looking at the impact of season on levels of depression and anxiety.

In their study, “depressed” hamsters that had been exposed to “short-day” periods exhibited fewer seeking behaviors. They were slower to enter open areas of a maze, slower to seek food, and gave up more quickly on a “forced swim test”, which is typically used as a measure of behavioral despair in rodents.

“Monitoring the changes in day length permits individuals to anticipate changes in both physiology and behaviors that facilitate adaptation to a changing physical and social environment,” Prendergast explained. “What we view as seasonal depressive-like behaviors in non-human animal models may represent supremely adaptive behavioral responses to winter conditions in the wild.”

These adaptive behaviors would prevent animals from engaging in energetically wasteful activities over the winter, such as finding a

mate. Prendergast and Nelson surmised that photoperiodic regulation of reproduction might actually explain these behavioral effects, as anxiety has a reciprocal relationship with sexual behavior in rodents.

### A link between immune response and depression

Given his work on the impact of the immune system on behavior, as well as the impact of photoperiod on mood, Leah Pyter, a post-doctoral researcher in Prendergast’s lab, began to wonder whether other types of chronic diseases would show similar kinds of behavioral effects. In an exciting new study, Pyter discovered for the first time a biological link between depression and cancer. It has long been known that cancer patients tend to experience depression, but it has been unclear as to whether the depression was brought on primarily through learning of the diagnosis, subsequent chemotherapy treatment, or other biological mechanisms.

According to this study, tumors induce changes in gene expression in the hippocampus, a region implicated in emotion regulation. In the context of this study, rats with tumors that displayed these genetic changes were “more depressed” than rats without tumors under identical conditions. Depression was again measured using the “forced swim test” as well as a rat’s eagerness to consume sweetened water, a substance usually much sought after by healthy rats.

Moreover, the rats with tumors had elevated levels of cytokines in the brain and blood. Elevated levels of cytokines, cellular signaling molecules that are typically associated with the functioning of the immune system, had previously been linked to depression.

Prendergast seemed particularly excited to pursue this line of research given that it had been shown some years ago that there also exists a seasonal fluctuation in the likelihood of tumor formation in seasonally breeding animals, pointing once again to the fascinating interconnectedness between the immune system and photoperiod.

### A note of caution and future investigations

“We have to be careful about the comparisons we make between animal and human models. For example, the reproductive

physiology and behavior of humans do not depend on photoperiod as in the case with hamsters. In most cultures, humans copulate all year long,” cautioned Prendergast.

Regardless, even in laboratory rats, whose seasonal reproductive behavior has been bred out, seasonal fluctuations in the immune response are still observed, and it is possible that the mechanisms by which the immune system responds to photoperiod in a non-seasonal breeder might have some relevance for humans.

“I am interested in how our bodies decode melatonin signals. Do the immune and reproductive systems ‘listen’ to the signal in the same way?” mused Prendergast. He suspects that they do not, considering the fact that the immune system’s response to melatonin signaling may be quite rapid, whereas the response of the reproductive system is known to be quite slow.

“We are continuing to investigate the molecular mechanisms by which melatonin represents time in the central nervous system and in the immune system,” he added. “We are also very interested in pursuing questions rooted in behavioral immunology. For example, we are currently continuing to investigate tumor-induced changes in emotional tone, and we have seen some very interesting changes in higher-level cognitive processes, such as learning and memory, in response to tumor formation.” ■

BELOW: Brian Prendergast, Associate Professor in Psychology at the University of Chicago.



## RECENT PUBLICATIONS FROM THE PRENDERGAST LAB

**Baillie, SR, Prendergast, BJ. (2008).** Photoperiodic Regulation of Behavioral Responses to Bacterial and Viral Mimetics: A Test of the Winter Immunoenhancement Hypothesis. *Journal of Biological Rhythms*; 23(1):81-90.

**Paul MJ, Galang J, Schwartz WJ, Prendergast BJ. (2009).** Intermediate-duration day lengths unmask reproductive responses to nonphotic environmental cues. *Am J Physiol Regul Integr Comp Physiol*; 296(5):R1613-9.

**Prendergast BJ, Galang J, Kay LM, Pyter LM. (2009).** Influence of the olfactory bulbs on blood leukocytes and behavioral responses to infection in Siberian hamsters. *Brain Res.*; in press.

**Prendergast BJ. (2008).** Behavioral tolerance to endotoxin is enhanced by adaptation to winter photoperiods. *Psychoneuroendocrinology*; 33(4):540-5.

**Prendergast BJ, Kay LM. (2008).** Affective and adrenocorticotrophic responses to photoperiod in Wistar rats. *J Neuroendocrinol*; 20(2):261-7.

**Freeman DA, Kampf-Lassin A, Galang J, Wen JC, Prendergast BJ. (2007).** Melatonin acts at the suprachiasmatic nucleus to attenuate behavioral symptoms of infection. *Behav Neurosci*; 121(4):689-97.

