Brain circuit discovery illuminates circadian rhythms, psychiatric disorders with seasonal flare-ups

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Serotonin glows green in a microscope image of cells in the mouse brain stem. Credit: Giacomo Maddaloni

Harvard Medical School scientists have discovered a brain circuit that influences the ability to adapt to changes in day length, like those that occur from season to season or when traveling across time zones.
The study, based on research in mice and published July 17 in *Nature*, fills in another piece of the workings of circadian rhythms: the ways in which the brain adjusts behavior and body functions on a 24-hour cycle, based on external signals such as the presence and absence of daylight.

The work also reveals a new way brain cells can behave.

If affirmed in humans in further studies, the findings could help researchers understand the basis of mistimed sleep-wake and activity cycles, which can contribute to the development of certain diseases, including neurologic, heart, and metabolic disorders.

Further findings also could inform the design of treatments for people who struggle with sharp changes in day length or timing, such as shift workers and travelers, or people who have health conditions that are exacerbated by changes in day length or timing, including schizophrenia and seasonal affective, major depressive, and bipolar disorders.

"We know that solar light dictates organismal physiology and behavior, and that we have health issues if our body doesn't properly anticipate the light-dark cycle, but we tend to think about that on a daily scale, not seasonally," said Susan Dymecki, the George Fabyan Professor of Genetics in the Field of Comparative Pathology in the Blavatnik Institute at HMS, whose lab conducted the work.

"Finding a neural circuit that contributes significantly to the ability to adapt to changes in the day-night cycle is exciting," she said. "It would be wonderful if it can help us better understand how our brains work and how we might help people synchronize to those changes."

Furthermore, the researchers said, the results offer insights into how exposure to forms of artificial light at night, including digital screens, may confuse the brain's sense of day length and affect human health.
Part of a circadian circuit

The team—led by Giacomo Maddaloni, research fellow in genetics in the Dymecki lab—identified a brain circuit with multiple groups of neurons that together recognize, decode, and drive behavioral adaptation to changes in the amount of daylight.

Central to this circuit is a set of neurons dubbed mrEn1-Pet1. Maddaloni and colleagues found that these neurons receive signals from a brain region called the preoptic area, which is told directly about whether it's light or dark by nerve cells in the retina at the back of the eye.

The team determined that mrEn1-Pet1 neurons then send signals to three areas of the brain involved in circadian rhythms and sleep-wake patterns, including the body's master circadian clock, called the superchiasmatic nucleus or SCN.

This discovery placed the mrEn1-Pet1 neurons within a brain circuit that starts with light detection and continues to circadian rhythm regulation. But how were the neurons communicating, the researchers wondered.
A tale of two chemicals

Scientists already knew that mrEn1-Pet1 neurons release serotonin, a chemical involved in a myriad of functions from breathing rate to mood to appetite. Maddaloni and colleagues, however, found that mrEn1-Pet1 cells can likely also release the chemical glutamate, which activates neurons that receive it.

A common understanding among scientists has been that neurons that can release one or more chemicals do so to all the brain regions they "talk" to. To their surprise, Dymecki's team found that the mrEn1-Pet1 neurons deploy serotonin and glutamate independently—sometimes
together, sometimes separately, sometimes in different amounts—to the three brain regions they connect to.

"It's really cool, the mechanism these cells use," said Maddaloni.

The team's experiments indicated that the mrEn1-Pet1 neurons take the environmental cue of light or dark duration and change their deployment of serotonin and glutamate accordingly. This appears to provide information to the master circadian clock, which incorporates it with other inputs to decide whether it should adjust the animal's biological response and ultimately its behavior.

 Blocking various parts of the circuit impaired mice's ability to adjust to changes in day length. When the team made "day" length longer or shorter in the lab, mimicking summer or winter, mice with disruptions in the mrEn1-Pet1 system took much longer to sync their sleep and wake times to the new day length than normal mice and lagged in shifting their wheel-running activity to appropriate times and lengths.

"The results were really striking," said Maddaloni. "Mice kept waking up according to the previous light cycle. They were 'blind' to the changes in season."

When the mrEn1-Pet1 neurons are disrupted, the SCN doesn't adjust properly, confirmed Dymecki. She explained, "It affects a fundamental mechanism in the master circadian regulator."

Dymecki and Maddaloni want to find out whether this ability to deploy different neurotransmitters to different brain regions is unique to mrEn1-Pet1 neurons.

**From mouse to human**
How applicable the findings are to human health will depend on whether our brains have mrEn1-Pet1 neurons and a comparable circadian circuit.

Although her team hasn't yet looked for mrEn1-Pet1 cells in human brain tissue, Dymecki is encouraged by the fact that the neurons reside in the mouse brain stem, an evolutionarily ancient area that changes very little across mammals.

Another promising sign: Every time the team has looked in the human brain stem for other types of serotonin-releasing cells present in the mouse brain stem, they've found them.

Also, imaging studies have shown a link between abnormalities in this brain region in humans and conditions such as bipolar disorder, Dymecki said.

"We think the cells will be there," she said. "If they are, it would be very satisfying to add to our limited knowledge about how our brains evolved to synchronize to changes in light exposure and to possibly help mitigate the devastating effects that dysregulation of adaptation to day-length changes can have on people's health."


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