RESEARCHING FUNDAMENTAL **RHYTHMS** OF **LIFE**

Evolution has harmonized the behavior of humans and all other mammals with fundamental rhythms of life that include the cycle of light and dark experienced each day and with seasonal change. The brain's circadian clock controls hormone production related to natural patterns of sleeping/waking behavior which, when disrupted by experiences such as jet lag or night-shift work, can have adverse health effects. It's a vital physiological process intrinsic to our mood and alertness, but one that has yet to be fully understood.

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Assistant Professor Casey Diekman

A GROUP OF ABOUT 20,000 NEURONS IN THE HYPOTHALAMUS RECEIVES INFORMATION ABOUT THE LIGHT/DARK CYCLE FROM THE EXTERNAL WORLD THROUGH THE RETINA THAT CAN AFFECT THE CIRCADIAN PROCESS. THE JOB OF THIS PART OF THE BRAIN IS TO KNOW WHAT TIME OF DAY IT IS.

Gaining greater insight into the biological clock that sets the pace for daily life is the focus of a transatlantic research effort involving Casey Diekman, assistant professor in the Department of Mathematical Sciences. Diekman's work, which is being funded by a three-year grant of more than $233,000 from the National Science Foundation (NSF), could yield new knowledge for the U.S. national BRAIN Initiative – an acronym for Brain Research through Advancing Innovative Neurotechnologies.

MODEL CONTRIBUTIONS

Diekman joined the NJIT faculty in 2013, after post-doctoral work at the NSF-funded Mathematical Biosciences Institute at Ohio State University. His primary goal as the NSF grant's principal investigator is to develop mathematical models that will promote understanding of the role that our internal clock's electrical activity plays in circadian timekeeping, in particular the way the clock responds to the natural light/dark cycle.

Diekman is collaborating with Professor Hugh Piggins and Research Associate Mino Belle at the University of Manchester in England. Piggins' laboratory is providing experimental biological data about electrical activity in the brain at the cellular level, specifically with respect to the influence of dynamic changes in gene expression on neurons in the suprachiasmatic nucleus, or SCN. Gene expression is the process by which DNA is translated into proteins, and proteins are the engines of most physiological functions, including circadian behavior.

A group of about 20,000 neurons in the hypothalamus, the SCN receives information about the light/dark cycle from the external world through the retina that can affect the circadian process. "The job of this part of the brain is to know what time of day it is," Diekman says succinctly. It is a job that the SCN also may do without direct exposure to external light/dark conditions.

TWO VASTLY DIFFERENT TIME SCALES

At the neuronal level, the interplay of several ionic currents within SCN neurons produces electrical oscillations on the time scale of milliseconds. Ultimately, these electrical signals add up to our daily behavior patterns. Experimentally, the challenge has been to collect data about these currents under precisely controlled light/dark conditions in order to study how SCN activity may vary over a particular period, such as 24 hours. While collecting this data is a very labor-intensive process, it provides the raw material for Diekman's mathematical modeling.

A key goal of the resulting model is to integrate the experimental data into a comprehensive physiological portrait to simulate neuronal activity and clarify the discrete roles of various ionic currents, Diekman explains. And a major mathematical objective is to take information about biological events that occur on a millisecond time scale and determine how they collectively affect 24-hour behavioral patterns. The model can then be used to make predictions about the circadian time-keeping process that can be verified in the laboratory, and to suggest new experiments that will add to our knowledge in this area.

"We want to understand the interaction between two different biological 'oscillators' operating on two vastly different time scales," Diekman says.

Preliminary results obtained by Diekman and his research colleagues suggest that the circadian rhythms they are studying comprise a truly intrinsic process rooted in "hard-wired" neuronal electrical programming. More specifically, as suggested by Diekman's modeling, the neurons in the SCN will begin to enter a state where they are less active in the afternoon. In this state, the neurons' electrical activity has an especially pronounced effect on gene expression, influencing hormone production and other physiological indicators without external light/dark exposure. It is a rhythm deeply encoded in our DNA.

As a component of the BRAIN Initiative, Diekman's work has broader implications as well. He anticipates that deeper understanding of the flow of information involved at the cellular level will aid in the development of mathematical models of brain processes such as long-term memory formation. The project also could impact areas of mathematical biology beyond circadian rhythms by advancing development of computer-simulation methods capable of handling widely disparate time scales. ■

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