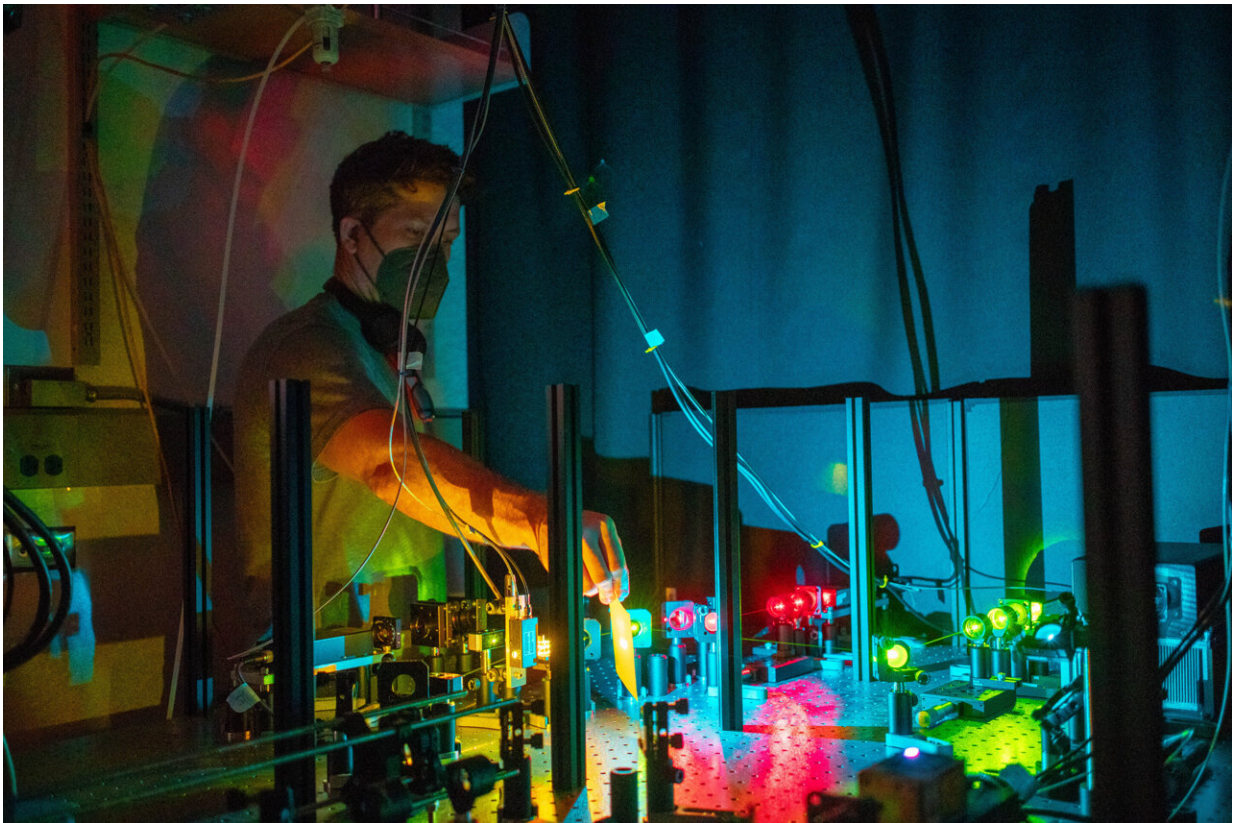


# 'Eye-opening' study sheds light on circadian pacemaker

October 27 2023

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Colenso Speer highlights a beam path on his group's custom-built instrument for super-resolution single-molecule localization microscopy. This microscope enables his team to visualize proteins within large tissue volumes with nanoscale image resolution. Credit: Nathaniel Underland

University of Maryland researchers studied synaptic changes in an

animal model before and after it developed vision, which plays a key role in circadian rhythm.

In a [new study](#) featured on the cover of the journal *Analytical Chemistry*, titled "Microanalytical Mass Spectrometry with Super-Resolution Microscopy Reveals a Proteome Transition During Development of the Brain's Circadian Pacemaker," a team of University of Maryland researchers used cutting-edge technologies to study a little-understood visual pathway in an [animal model](#).

The research team set out to understand how the development of vision affects proteins in a part of the brain called the suprachiasmatic nucleus (SCN), which is considered the main circadian pacemaker in mammals because of its ability to regulate circadian rhythms in response to light.

Designed by Peter Nemes, a professor in the Department of Chemistry and Biochemistry, and Colenso Speer, an assistant professor in the Department of Biology, the study stems from a 2019 seed grant from UMD's Brain and Behavior Institute (BBI) that also included Cell Biology and Molecular Genetics Professor Najib El-Sayed. Nemes previously received a Beckman Young Investigator award from the Arnold and Mabel Beckman Foundation in 2015, which enabled the construction of the mass spectrometer that Nemes further refined at UMD for this latest project.

Their study fused two advanced and disparate technologies: mass spectrometry and microscopy.

"The BBI award was so important for Colenso and me because it allowed us to get together and integrate these totally different disciplines," Nemes said. "I work in chemistry with mass spectrometry, which can identify and quantify up to a thousand different proteins in a neuron. With [high-resolution microscopy](#), Colenso can zoom into tissue—down

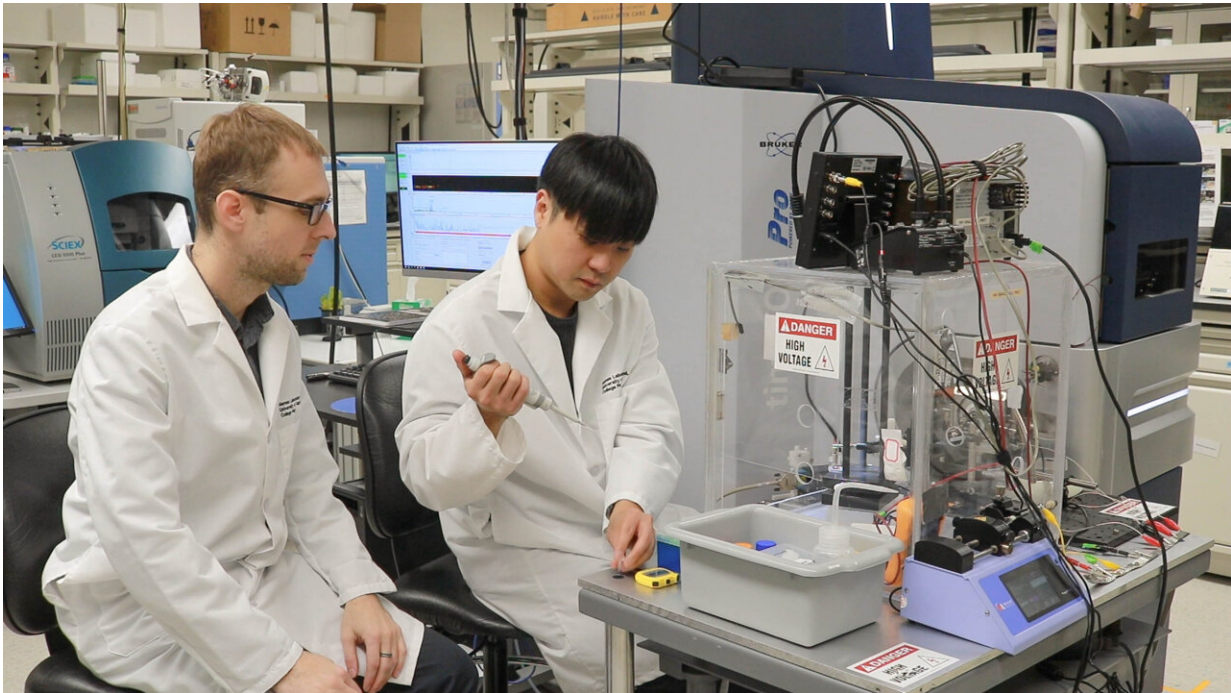
to the level of single cells, axons and dendrites—and provide exquisite spatial resolution."

With the ability to pinpoint where synapses are forming, the research team determined that various proteins increased in production when a mouse opened its eyes for the first time—an important developmental stage linked to circadian rhythm.

Levels of a protein called synapsin spiked after eye opening due to the growth of new synapses, but they did not come from the retina. Instead, they likely originated in the hypothalamus—the region of the brain that houses the circadian pacemaker.

"These findings tell us that there are different mechanisms of synaptic organization and development in distinct visual circuits critical for behavior and physiology," Speer said. "Understanding these differences in synaptic specificity and development is a critical step toward understanding the many ways that light regulates brain function outside of what we normally think of as vision."

Their study is the first to identify proteins and image synapses in a mouse's SCN at such an early developmental stage. While they focused on a specific visual pathway, Nemes and Speer said that researchers have a broader interest in understanding the circadian pacemaker, in part because of its importance to [human health](#).



Peter Nemes and Sam Choi prepare the proteome of the suprachiasmatic nucleus for mass spectrometry analysis. This custom-built tool can detect thousands of different proteins from limited tissue and cell microenvironments. Credit: Nathaniel Underland

"There are human health concerns with circadian physiology, most notably shift work disorder," Speer said. "A common one that we all suffer from at some point is jet lag, which is a disconnect between your body's intrinsic circadian rhythm and the light cycle of the new location that you find yourself in."

Speer noted that the technologies he and Nemes developed could be applied to a wide range of studies. In the future, they could even extend to research on human health and disease.

"We could envision opportunities for applying this type of imaging



technology and mass spectrometry to biopsied or postmortem samples as preclinical research to help establish the commonalities and differences between human neural circuits and these animal models that we're working on in the laboratory," Speer said. "I think this opens up a lot of exciting opportunities in terms of understanding how local proteins in synapses are regulated."

Nemes is excited to see how their blended technologies will be applied in future research, adding that their *Analytical Chemistry* paper is just the beginning.

"By integrating ultra-high-sensitivity [mass spectrometry](#) with super-resolution imaging to discover new findings, you could apply this to any other context in the brain," Nemes said. "This work lays the foundation for many more studies to come."

**More information:** Sam B. Choi et al, Microanalytical Mass Spectrometry with Super-Resolution Microscopy Reveals a Proteome Transition During Development of the Brain's Circadian Pacemaker, *Analytical Chemistry* (2023). [DOI: 10.1021/acs.analchem.3c01987](https://doi.org/10.1021/acs.analchem.3c01987)

Provided by University of Maryland

Citation: 'Eye-opening' study sheds light on circadian pacemaker (2023, October 27) retrieved 29 April 2024 from <https://phys.org/news/2023-10-eye-opening-circadian-pacemaker.html>

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