Scientists focus on glymphatic system and its role in sleep, memory consolidation, degenerative illnesses

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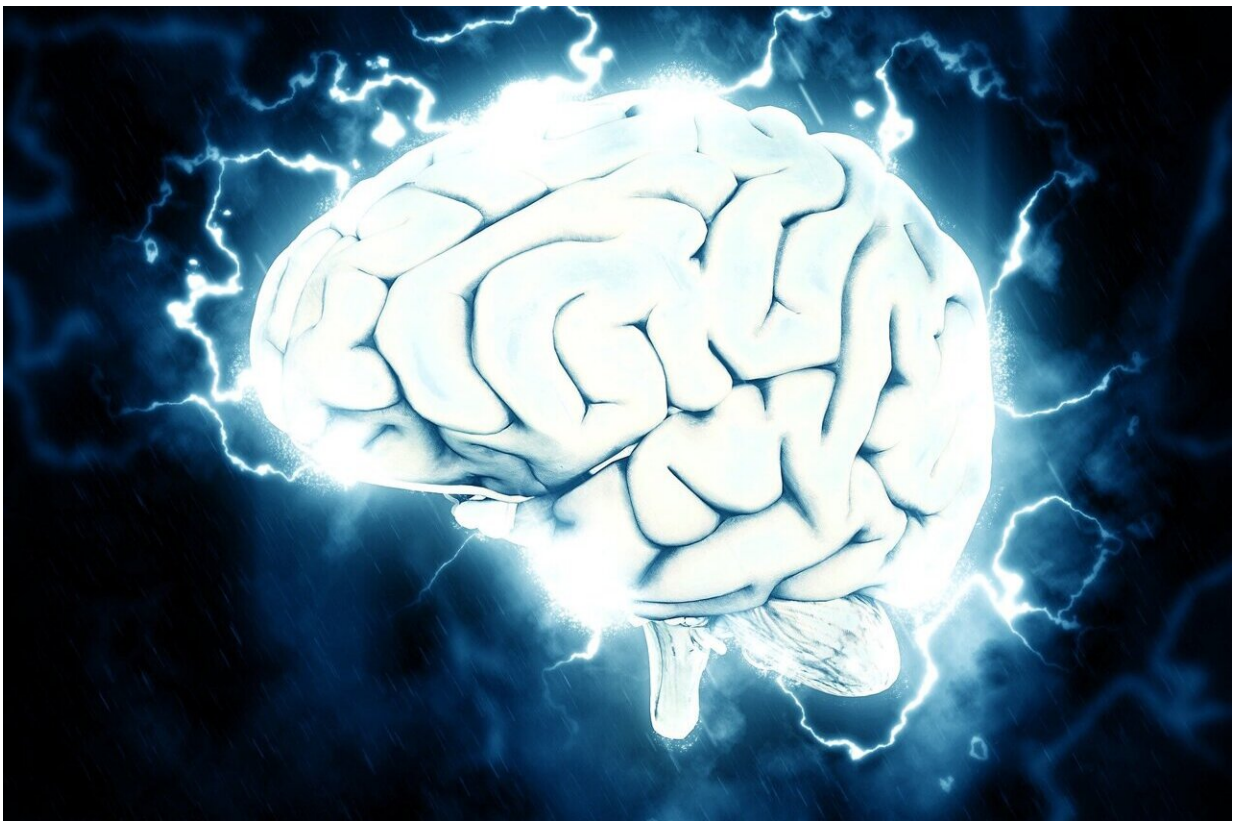

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When we think of brains, we tend to think of neurons. It's right there in our word for the study of the brain: neuroscience. But when it comes to

certain mysteries of the brain—for example, the role of sleep in memory consolidation, or the genesis of traumatic brain injuries (TBIs) and degenerative neurological disorders such as Parkinson's disease and Alzheimer's disease—the answers we seek may lie elsewhere: the glymphatic system.

A waste clearance system for the brain and the nervous system of humans and other vertebrates, the glymphatic system derives its name from the brain's glial cells, on which it depends, and the lymphatic system, which it resembles functionally. It consists of the pathway including channels called ventricles, the brain's interstitial spaces—the spaces between the cells in the brain's gray and white matter—and the perivascular spaces around veins and arteries in the brain.

Scientists at the Johns Hopkins Applied Physics Laboratory (APL) in Laurel, Maryland, are working to advance our understanding of the glymphatic system and the role it plays in sleep, memory consolidation, degenerative illnesses and more.

Reawakened interest, 150 years later

"If you go back to neuroimaging all the way back to the 1850s, scientists were primarily interested in imaging the ventricles to better understand pathologies like hydrocephalus [a neurological disorder caused by a buildup of excess cerebrospinal fluid (CSF)]," said Clara Scholl, chief scientist of the Neuroscience Group in APL's Research and Exploratory Development Department (REDD). "And then neurons were discovered, and the focus shifted away from the ventricles and toward cellular matter in the brain for the next 150 years or so."

In the past decade, studies with fluorescent tracers in mice led to the discovery of the glymphatic system and its role in sleep and neurodegenerative disease, among other questions. "The field has

developed a solid understanding of how this system works through animal models, as well as invasive studies in humans in which they inject dyes into the CSF and then observe sleeping subjects using MRI [magnetic resonance imaging] scanners," Scholl said.

It's clear by now that a better understanding of the glymphatic system—how it functions, how to observe and influence its workings—could have a significant and positive impact on human health, in a variety of civilian and military applications. But before that can happen, significant technology gaps will have to be addressed.

"If you have a pathology in your glymphatic system, we have no way to determine that without injecting fluorescent tracers into your CSF or putting you in an MRI scanner while you're sleeping," said Scholl, "Or in some conditions, you might have a hole drilled in your skull to relieve the pressure and a sample of your CSF can be taken in the process. But there's really no noninvasive way to observe or measure CSF flow dynamics in the brain. That's where APL comes in."

From phantoms to humans

APL's work in glymphatic system sensing began with an effort to use commercial off-the-shelf sensors to track its role in TBI. Sponsored by Uniformed Services University (USU) and supported by the Congressionally Directed Medical Research Programs (CDMRP), this project is a collaboration with Navy sleep physician J. Kent Werner. The potential they saw using noninvasive, near-infrared spectroscopy sensors (NIRS)—a technology traditionally used for tracking hemodynamic activity (blood flow)—inspired the APL team to extend its capabilities.

Within a relatively short period of time, Scholl and the rest of the APL team, guided by the expertise of REDD optical physicist Joseph Angelo, have applied a specialized form of NIRS, known as frequency domain

functional NIRS (FD-fNIRS), to develop noninvasive sensors that can accurately track the activity of the glymphatic system.

To tune FD-fNIRS to observe the complex fluid dynamics of the glymphatic system, the APL team developed "optical phantoms" that model the optical properties of the glymphatic system—an effort described in a publication in *IEEE Xplore* based on a conference paper. Since that accomplishment, Will Coon, a sleep scientist and neural signals engineer in REDD, has gone on to conduct sleep studies in which glymphatic activity was measured and tracked alongside more traditional metrics associated with sleep, such as electroencephalographic (EEG) activity.

Establishing correspondence between the glymphatic system and the known dynamics of sleep is no small feat, but it's worth the effort. "There's good reason to believe we can interact with the glymphatic system," Coon said. "We know the drivers. We're starting to see that a particular kind of sleep called slow-wave sleep stimulates blood flow into the brain. And when blood flows in, CSF flows out—that seems to be the driver for much of the glymphatic system's waste clearance activity."

Coon continued, "Fortunately, there's an extensive body of research around slow-wave sleep and memory consolidation—we know ways to interact with and control these slow waves, how to increase them, like using clicks and sounds to stimulate more waves. And if we can do that, it points to possible treatments for the glymphatic system—maybe treatments we can apply preventatively with TBI in order to stave off neurological decline 20 or 30 years down the road."

A cold trail revived

Recently, APL began a collaboration with Michael Smith, a sleep doctor

at Johns Hopkins Medicine (JHM) in Baltimore. Smith came across a trio of research papers from the late 1980s that found that cooling delivered at specific moments during sleep could induce extended bouts of slow-wave sleep in human subjects. Those findings were replicated not long ago by several European research teams, which brought them to Smith's attention.

"This is an exciting discovery, because using sound-based methods, you can only turn one or two slow waves into five or six waves; but this thermal effect has the potential to induce hundreds, maybe even thousands of slow waves, which adds up to significantly more restorative slow-wave sleep," Coon explained. "That could be a game-changer for helping aging populations achieve better glymphatic clearance, including healthy people and those with neurological disorders, including Alzheimer's and Parkinson's."

Reaching for the STARS: A comprehensive sleep ecosystem

Coon conducts research at APL targeted at achieving a comprehensive understanding of sleep. To build that understanding, he is leading efforts to invent new technologies that can influence or fine-tune sleep to achieve a variety of objectives—whether treating neurodegenerative disorders, helping soldiers thrive on less sleep, understanding the role of sleep in fatigue or improving human memory.

This suite of technologies goes by the name STARS: System to Augment Restorative Sleep, said Coon, "STARS is intended to encompass a hardware and software ecosystem that allows us to incorporate various technologies—commercial smart rings and wearables, APL-developed thermoelectric devices—and that can scale to meet specific sponsor constraints, whether that's software, power, practicality or cost."

"The engineering world and the clinical sleep world traditionally sit almost entirely apart from one another," Coon said. "That's why it's so cool to work at a place like APL, where we can collaborate with JHM, and we have—thanks to [Scholl]—a team of people who have years of experience studying sleep, and are also engineers. We have a real opportunity before us to revolutionize the field, and our work with the glymphatic system is just the beginning."

More information: Joseph P. Angelo et al, Optical Phantoms for Calibrating a Novel Neuroimaging System Targeting Central Nervous System Fluid Flow Dynamics, *2023 11th International IEEE/EMBS Conference on Neural Engineering (NER)* (2023). DOI: 10.1109/NER52421.2023.10123860

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