Scientists discover neurons help flush waste out of brain during sleep

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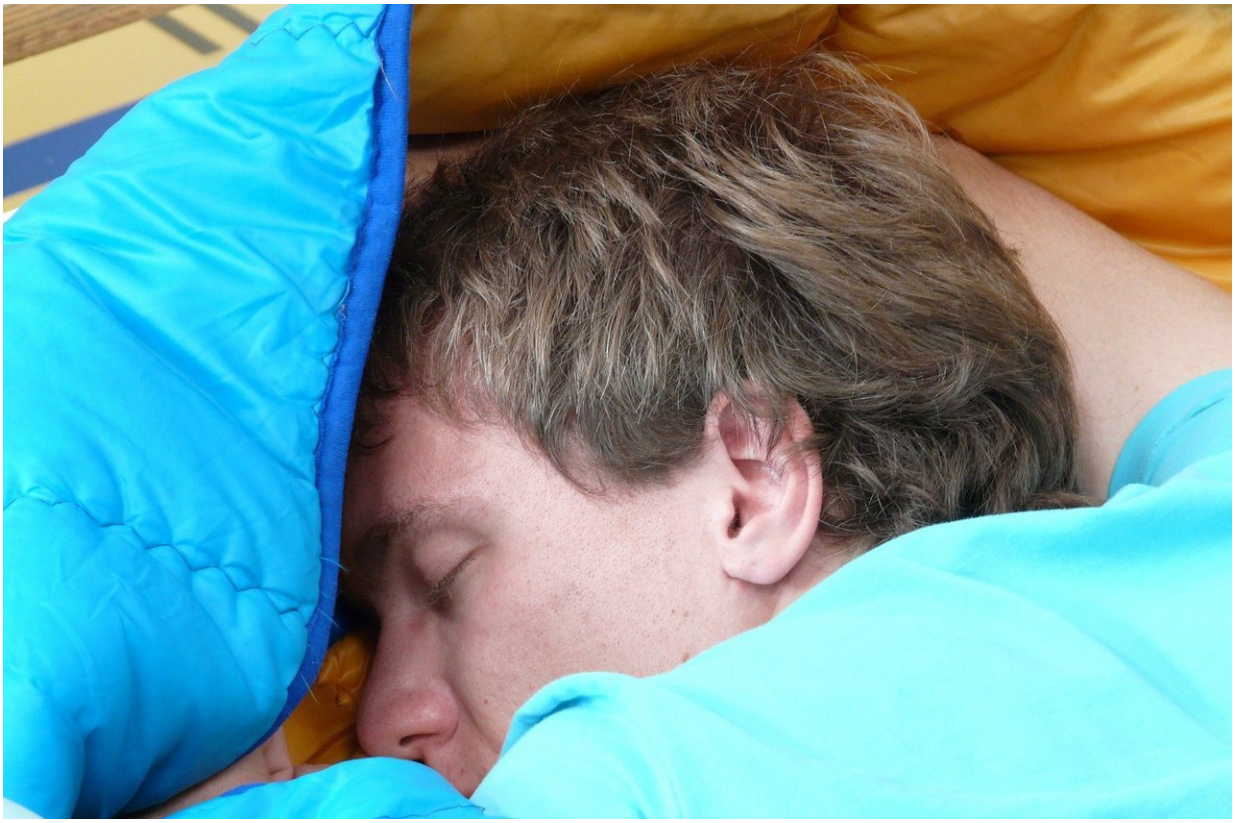

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There lies a paradox in sleep. Its apparent tranquility juxtaposes with the brain's bustling activity. The night is still, but the brain is far from dormant. During sleep, brain cells produce bursts of electrical pulses that

cumulate into rhythmic waves—a sign of heightened brain cell function.

But why is the brain active when we are resting?

Slow brain waves are associated with restful, refreshing sleep. And now, scientists at Washington University School of Medicine in St. Louis have found that brain waves help flush waste out of the brain during sleep. Individual nerve cells coordinate to produce rhythmic waves that propel fluid through dense brain tissue, washing the tissue in the process.

"These neurons are miniature pumps. Synchronized neural activity powers fluid flow and removal of debris from the brain," explained first author Li-Feng Jiang-Xie, Ph.D., a postdoctoral research associate in the Department of Pathology & Immunology.

"If we can build on this process, there is the possibility of delaying or even preventing neurological diseases, including Alzheimer's and Parkinson's disease, in which excess waste—such as metabolic waste and junk proteins—accumulate in the brain and lead to neurodegeneration."

The findings are published Feb. 28 in *Nature*.

Brain cells orchestrate thoughts, feelings and body movements, and form dynamic networks essential for memory formation and problem-solving. But to perform such energy-demanding tasks, brain cells require fuel. Their consumption of nutrients from the diet creates metabolic waste in the process.

"It is critical that the brain disposes of metabolic waste that can build up and contribute to neurodegenerative diseases," said Jonathan Kipnis, Ph.D., the Alan A. and Edith L. Wolff Distinguished Professor of Pathology & Immunology and a BJC Investigator. Kipnis is the senior author on the paper.

"We knew that sleep is a time when the brain initiates a cleaning process to flush out waste and toxins it accumulates during wakefulness. But we didn't know how that happens. These findings might be able to point us toward strategies and potential therapies to speed up the removal of damaging waste and to remove it before it can lead to dire consequences."

But cleaning the dense brain is no simple task. Cerebrospinal fluid surrounding the brain enters and weaves through intricate cellular webs, collecting toxic waste as it travels. Upon exiting the brain, contaminated fluid must pass through a barrier before spilling into the lymphatic vessels in the dura mater—the outer tissue layer enveloping the brain underneath the skull. But what powers the movement of fluid into, through and out of the brain?

Studying the brains of sleeping mice, the researchers found that neurons drive cleaning efforts by firing electrical signals in a coordinated fashion to generate rhythmic waves in the brain, Jiang-Xie explained. They determined that such waves propel the fluid movement.

The research team silenced specific brain regions so that neurons in those regions didn't create rhythmic waves. Without these waves, fresh cerebrospinal fluid could not flow through the silenced brain regions and trapped waste couldn't leave the brain tissue.

"One of the reasons that we sleep is to cleanse the brain," Kipnis said.

"And if we can enhance this cleansing process, perhaps it's possible to sleep less and remain healthy. Not everyone has the benefit of eight hours of sleep each night, and loss of sleep has an impact on health. Other studies have shown that mice that are genetically wired to sleep less have healthy brains. Could it be because they clean waste from their brains more efficiently? Could we help people living with insomnia by

enhancing their brain's cleaning abilities so they can get by on less sleep?"

Brain wave patterns change throughout sleep cycles. Of note, taller brain waves with larger amplitude move fluid with more force. The researchers are now interested in understanding why neurons fire waves with varying rhythmicity during sleep and which regions of the brain are most vulnerable to waste accumulation.

"We think the brain-cleaning process is similar to washing dishes," neurobiologist Jiang-Xie explained.

"You start, for example, with a large, slow, rhythmic wiping motion to clean soluble wastes splattered across the plate. Then you decrease the range of the motion and increase the speed of these movements to remove particularly sticky food waste on the plate. Despite the varying amplitude and rhythm of your hand movements, the overarching objective remains consistent: to remove different types of waste from dishes. Maybe the brain adjusts its cleaning method depending on the type and amount of waste."

More information: Jonathan Kipnis, Neuronal dynamics direct cerebrospinal fluid perfusion and brain clearance, *Nature* (2024). DOI: 10.1038/s41586-024-07108-6.
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