Neural sleep patterns emerged at least 450 million years ago, researchers find

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Researchers at the Stanford University School of Medicine have found that neural signatures in sleeping zebrafish are analogous to those of humans, suggesting that the brain activity evolved at least 450 million years ago, before any creatures crawled out of the ocean.

Scientists have known for more than 100 years that fish enter a sleeplike state, but until now they didn't know if their sleep resembled that of land animals.

The researchers found that when zebrafish sleep, they can display two

states that are similar to those found in mammals, reptiles and birds: slow-wave sleep and paradoxical, or rapid eye movement, sleep. The discovery marks the first time these brain patterns have been recorded in fish.

"This moves the evolution of neural signatures of sleep back quite a few years," said postdoctoral scholar Louis Leung, Ph.D.

A paper describing the research will be published July 10 in *Nature*. Philippe Mourrain, Ph.D., associate professor of psychiatry and behavioral sciences, is the senior author. Leung is the lead author.

To study the zebrafish, common aquarium dwellers also known as danios, the researchers built a benchtop fluorescent light-sheet microscope capable of full-fish-body imaging with single-cell resolution. They recorded brain activity while the fish slept in an agar solution that immobilized them. They also observed the heart rate, eye movement and muscle tone of the sleeping fish using a fluorescence-based polysomnography that they developed.

They named the sleep states they observed "slow-bursting sleep," which is analogous to slow-wave sleep, and "propagating-wave sleep," analogous to REM sleep. Though the fish don't move their eyes during REM sleep, the brain and muscle signatures are similar. (Fish also don't close their eyes when they sleep, as they have no eyelids.)

Sleeping like the fish

The researchers found another similarity between fish and human sleep. By genetically disrupting the function of melanin-concentrating hormone, a peptide that governs the sleep-wake cycle, and observing neural expressions as the fish slept, the researchers determined that the hormone's signaling regulates the fish's propagating wave sleep the way

it regulates REM sleep in mammals.

Other aspects of their sleep state are similar to those of land vertebrates, Mourrain said: The fish remain still, their muscles relax, their cardio-respiratory rhythms slow down and they fail to react when they're approached.

"They lose muscle tone, their heartbeat drops, they don't respond to stimuli—the only real difference is a lack of rapid eye movement during REM sleep," Mourrain said, though he added, "The rapid movement of the eyes is not a good criterion of this state, and we prefer to call it paradoxical sleep, as the brain looks awake while one is asleep."

While scientists can't say for certain that all animals sleep, it appears to be a universal need among vertebrates and invertebrates. Animals will die if they are deprived of sleep long enough, and people who fail to receive adequate sleep suffer from mental problems such as memory lapses and impaired judgment, along with a higher risk of disorders such as obesity and high blood pressure.

The exact benefits of sleep are still a mystery, however. "It's an essential function," Mourrain said, "but we don't know precisely what it does."

He added that sleep disorders are linked to most neurological disorders such as autism spectrum disorders, Fragile X syndrome, and Alzheimer's and Parkinson's disease. "Sleep disturbances are an aggravating factor of these disorders," Mourrain said. It is critical to develop this animal model to study sleep functions at the cellular level, including neuronal connectivity and DNA repair, and in turn understand the pathophysiological consequences of sleep disruptions, he added.

The discovery means sleep research can be conducted on zebrafish, which are easy to study, in part because they're transparent. They breed

quickly, are inexpensive to care for and are just over an inch long. Drug testing requires only the addition of chemicals to their water.

"Because the fish neural signatures are in essence the same as ours, we can use information about them to generate new leads for drug trials," Leung said. He added that mice, often a stand-in for human research, are nocturnal and a less relevant model for our sleep.

"As zebrafish are diurnal like humans, it's perhaps more biologically accurate to compare fish sleep with humans' for some aspects," Leung said.

More information: Neural signatures of sleep in zebrafish, *Nature* (2019). DOI: 10.1038/s41586-019-1336-7 , www.nature.com/articles/s41586-019-1336-7

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