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Red blood cell 'traffic' contributes to changes in brain oxygenation

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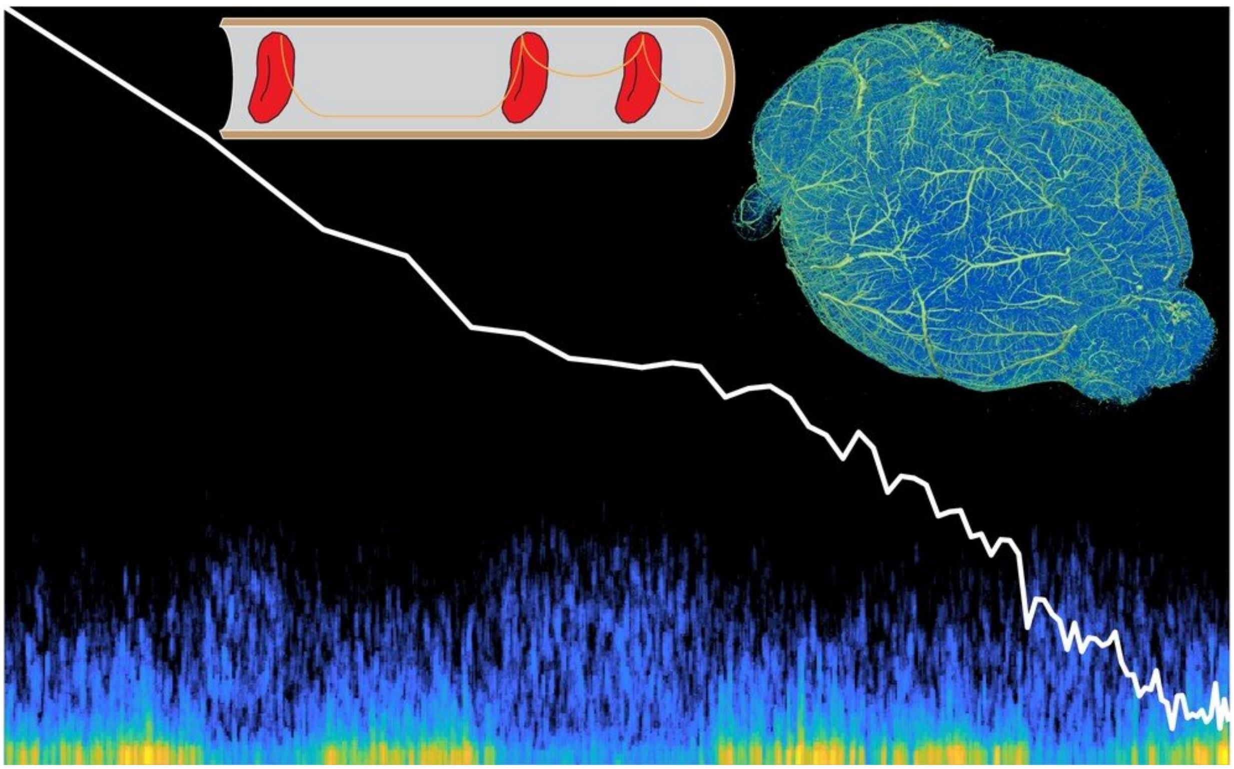

The researchers found that red blood cell "traffic" (top grey bar) appears to contribute to oxygenation fluctuations (white line), which are not correlated to changes in neural activity (bottom blue peaks) in mice brains (top right). Credit: Drew Lab and Yongsoo Kim Lab

Adequate blood flow supplies the brain with oxygen and nutrients, but the oxygenation tends to fluctuate in a distinct, consistent manner. The root of this varied activity, though, is poorly understood.

Now, Penn State researchers have identified one cause of the fluctuations: inherent randomness in the flow rate of red blood cells through tiny blood vessels called capillaries. According to the researchers, this randomness could have potential implications for understanding the biological build-up mechanisms underlying neurodegenerative diseases, such as Alzheimer's disease. They published their findings in *PLOS Biology* today.

"These oxygenation fluctuations also occur in other tissues, like muscle," said Patrick Drew, Huck Distinguished Associate Professor of Engineering Science and Mechanics, Neurosurgery and Biomedical Engineering. "The question we had was: Are these fluctuations caused by neural activity or something else?"

The fluctuations resemble 1/f-like noise, a statistical pattern showing large fluctuations made up of many small fluctuations and naturally occurring in a variety of phenomena, from stock-market prices to river heights. The researchers investigated the fluctuations in mice due to their brains' similarities to those of humans, according to Drew, who also serves as associate director of the Penn State Neuroscience Institute.

First, the researchers monitored the blood flow, oxygenation and electrical signals produced by brain activity—the first time the latter two had been tracked simultaneously, according to Drew—in awake mice. They collected the data as mice moved on a spherical treadmill for up to 40 minutes at a time.

Next, to investigate the relationship between brain activity and oxygenation fluctuations, the researchers used pharmacological compounds to temporarily and reversibly silence neural signals in the mice's brains. Despite the silencing, the fluctuations continued, showing little correlation between neural activity and oxygenation.

The passage of red blood cells, however, told a different story. Using two-photon laser scanning microscopy, an imaging technique used to visualize cells deep inside living tissue, the researchers could visualize the passage of individual red blood cells through capillaries.

"It's like traffic," Drew said. "Sometimes there are a lot of cars going by, and the traffic gets plugged up, and sometimes there aren't. And red blood cells go either way when they approach a junction, so this random flow can lead to bottlenecks and stalls in the vessel."

Importing experimental data into a statistical model allowed the researchers to run further simulations and make inferences based on massive amounts of data produced by the model. The researchers discovered that these random red blood cell stoppages contributed to the fluctuations in oxygenation, further supporting a relationship between the flow of red blood cells through capillaries and the tiny changes in oxygenation that formed larger trends.

Better understanding the regulation of blood flow and subsequent transport of oxygen can help researchers improve medical technology and explore causes of diseases such as Alzheimer's, according to Drew. While the researchers identified the link between red blood cell transport and oxygenation, further research is needed to investigate additional contributors to oxygenation fluctuations that could play a role in neurodegenerative diseases.

Kyle Gheres, a graduate student in the intercollege Graduate Program in Molecular Cellular and Integrative Biosciences, also contributed to this paper. Qingguang Zhang, assistant research professor of engineering science and mechanics, served as first author on the paper. This work was supported by the National Institutes of Health.

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