# New study uncovers vivid patterns of neural activity in the resting mouse brain

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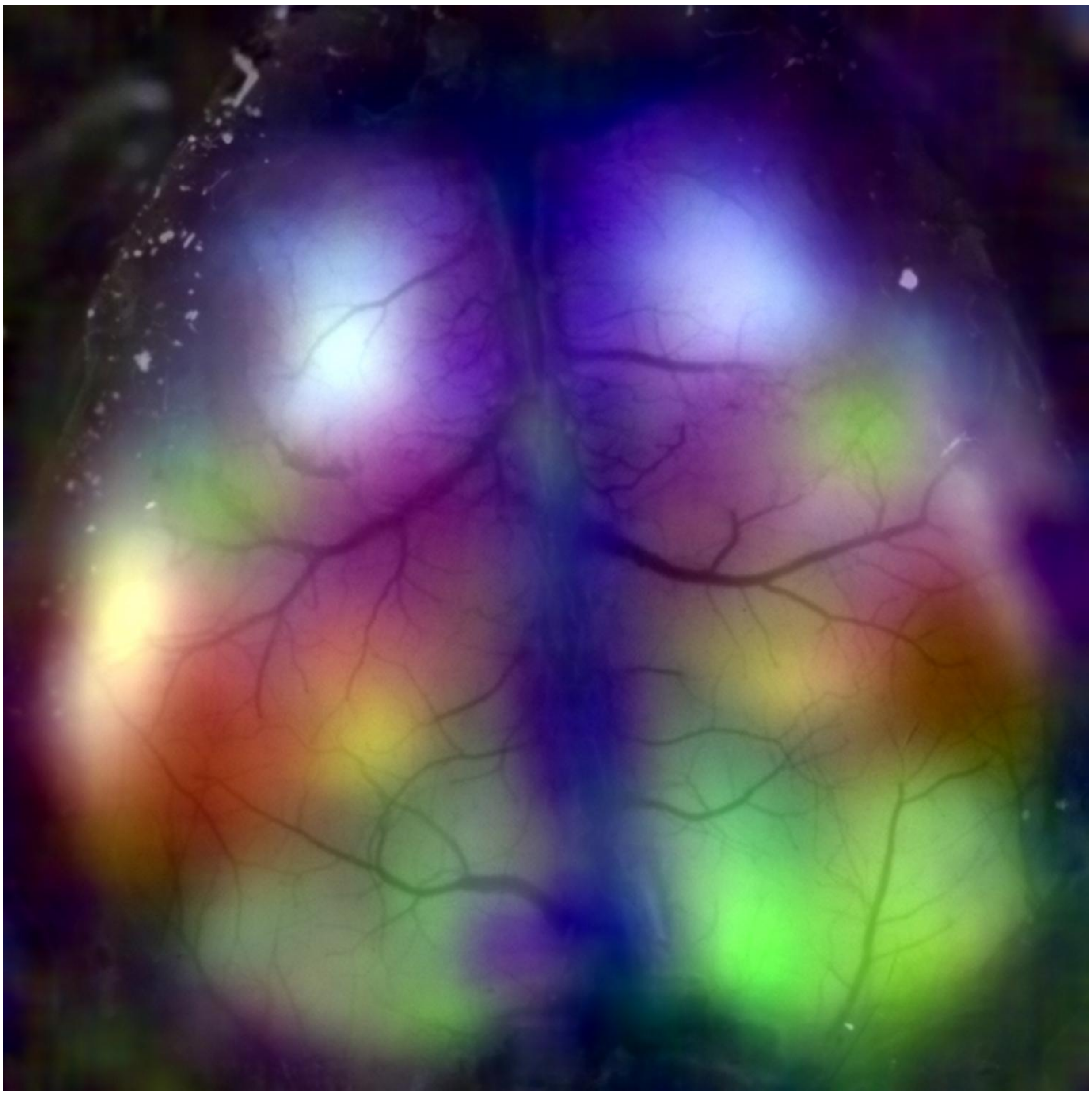

Image composite showing patterns of spontaneous neural activity occurring across the bilateral cortex of an awake mouse. Colors indicate different patterns of activity over time overlaid on a steady-state grayscale image. Credit: Ying Ma and Elizabeth Hillman/Columbia's Zuckerman Institute

Columbia scientists have traced the origins of mysterious signals in the brain that have captivated the functional magnetic resonance imaging (fMRI) community for the last decade. Using a recently developed imaging technique in mice, the Columbia team revealed synchronized, network-like neural activity coursing around the brain, even when the mouse was 'at rest.'

The researchers further demonstrated that this neural activity could predict slowly changing patterns of blood flow in the brain, connecting their findings to the enigmatic signals detected in so-called 'resting-state' fMRI. Taken together, this research provides a tantalizing new view of brain-wide neural activity that could lead to a better understanding of how distinct brain regions interact with each other, and how these connections—and the way they change with disease—can be studied in the human brain using fMRI.

The researchers published their findings today in the *Proceedings of the National Academy of Sciences*.

"Our results should reassure scientists in the resting-state fMRI community who have long believed that they were detecting patterns of neural activity," said Elizabeth Hillman, PhD, principal investigator at Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute, associate professor of biomedical engineering and radiology at Columbia's Fu Foundation School of Engineering and Applied Science and the paper's senior author. "At the same time, our results may come as a surprise for those who have remained skeptical that—first of all—this type of underlying neural activity even exists, but also that such activity can be accurately represented by fMRI signals."

Within a few years of the first demonstration of fMRI, scientists noticed that, even without an external stimulus, fluctuating signals could be detected in the brains of humans. Despite appearing to be random, analysis of these signals identified regions located on opposite sides of the brain that were synchronously singing the same random song. This synchrony was taken as evidence of interconnected functional networks throughout the brain. Moreover, properties of these networks were found to distinguish subtle signs of disease that are otherwise undetectable. However, these resting-state fMRI signals have proved challenging to interpret, in large part because fMRI works not by tracking the activity of neurons in the brain, but by tracking changes in blood flow as a proxy for that activity. As a result, it has been difficult to reconcile this high-level view of the brain with how scientists think of neurons interacting with each other individually.

To address this, Dr. Hillman and her team employed a wide-field, optical imaging method that allowed them to visualize both changes in blood flow and neural activity simultaneously across the surface of the mouse brain. Much to their surprise, they saw patterns of neural activity that flickered and swirled around the brain in elegant symmetric patterns.

"First, we only looked at small areas of the brain, seeing what seemed to be flashes and random activity,"said Dr. Hillman. "But when we zoomed out to view both sides of the brain at once, we saw that this activity wasn't random—it was symmetrical, organized and composed of repeating patterns. We immediately thought of resting-state fMRI."

They then compared these patterns to changes in blood flow. And while these blood-flow changes at first appeared sluggish compared to the neural activity, further analysis revealed that the fluctuations did in fact represent a cumulative effect; each small neural signal was triggering a small, slow increase in blood flow.

"In essence, these findings tell us that resting-state fMRI is probably picking up a representation of these underlying neural signals," said Ying Ma, a doctoral candidate at Columbia and the paper's first author. "What is great about our data is that it lets us uncover how these signals get blurred and distorted in fMRI, and whether there are any additional changes in blood flow—or cellular activity—that are also occurring but that aren't accounted for by normal neural activity. We hope that this will help to improve how fMRI data is analyzed and interpreted."

The team has already begun working with fMRI researchers to help in the development of more robust methods of drawing information out of resting-state fMRI scans in the healthy human brain, and to explore how and why networks appear to change in disease states.

Moving forward, Dr. Hillman and her team are also expanding their studies of brain-wide neural activity to include more complex methods that, she hopes, will provide fundamental insights into how and why this resting-state neural activity is generated.

"Our high-speed imaging methods are giving us an entirely new view of what the brain is doing, one that we hadn't seen before," said Dr. Hillman. "We are eager to understand how this brain-wide activity fits with classic descriptions of the brain's underlying circuitry.

"Moreover," she added, "we can follow the lead of resting-state fMRI and understand why these activity patterns are affected by disease, this could be the first step to developing new treatments."

**More information:** Resting-state hemodynamics are spatiotemporally coupled to synchronized and symmetric neural activity in excitatory neurons, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1525369113

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