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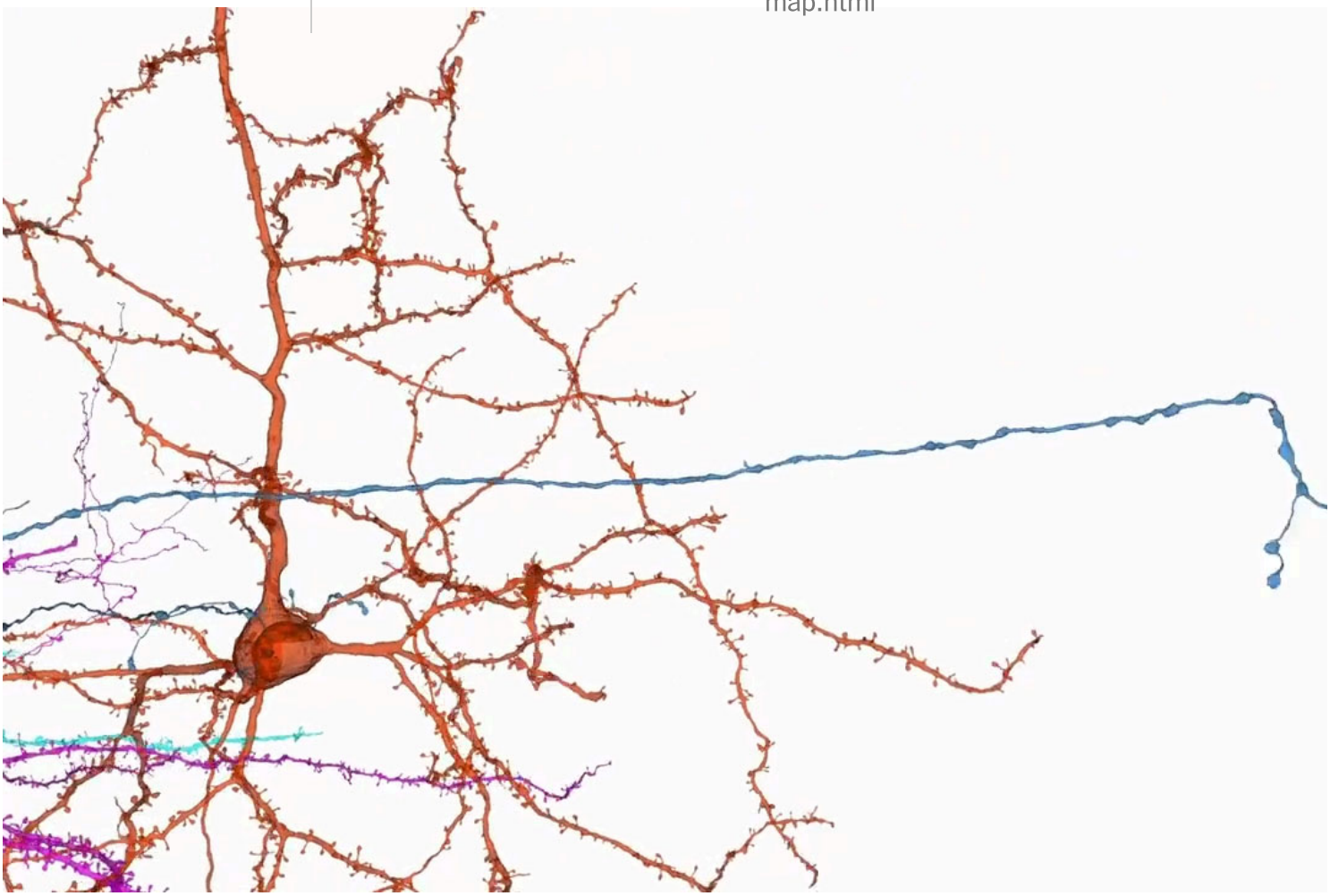

An Advance in Brain Research That Was Once Considered Impossible

Scientists achieved “a milestone” by charting the activity and structure of 200,000 cells in a mouse brain and their 523 million connections.

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By Carl Zimmer

April 9, 2025

The human brain is so complex that scientific brains have a hard time making sense of it. A piece of neural tissue the size of a grain of sand might be packed with hundreds of thousands of cells linked together by miles of wiring. In 1979, Francis Crick, the Nobel-prize-winning scientist, concluded that the anatomy and activity in just a cubic millimeter of brain matter would forever exceed our understanding.

“It is no use asking for the impossible,” Dr. Crick wrote.

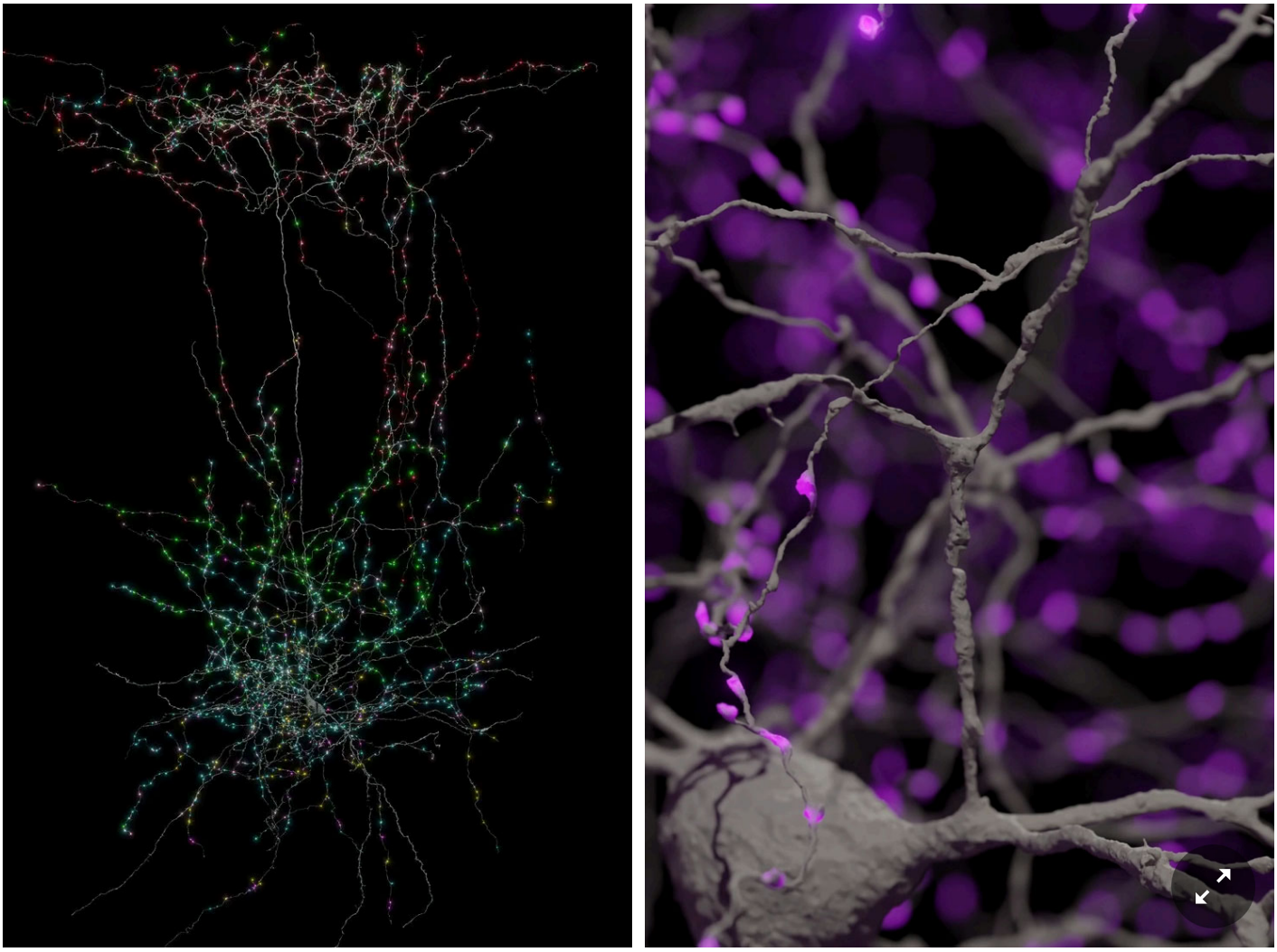
Forty-six years later, a team of more than 100 scientists has achieved that impossible, by recording the cellular activity and mapping the structure in a cubic millimeter of a mouse’s brain — less than one percent of its full volume. In accomplishing this feat, they amassed 1.6 petabytes of data — the equivalent of 22 years of nonstop high-definition video.

“This is a milestone,” said Davi Bock, a neuroscientist at the University of Vermont who was not involved in the study, which was published Wednesday in the journal Nature. Dr. Bock said that the advances that made it possible to chart a cubic millimeter of brain boded well for a new goal: mapping the wiring of the entire brain of a mouse.

“It’s totally doable, and I think it’s worth doing,” he said.

More than 130 years have passed since the Spanish neuroscientist Santiago Ramón y Cajal first spied individual neurons under a microscope, making out their peculiar branched shapes. Later generations of scientists worked out many of the details of how a neuron sends a spike of voltage down a long arm, called an axon. Each axon makes contact with tiny branches, or dendrites, of neighboring neurons. Some neurons excite their neighbors into firing voltage spikes of their own. Some quiet other neurons.

Human thought somehow emerges from this mix of excitation and inhibition. But how that happens has remained a tremendous mystery, largely because scientists have been able to study only a few neurons at a time.



One type of cell mapped by the scientists, called a Martinotti cell, sends out inhibitory signals that dampen the activity of other neurons in the brain.

In recent decades, technological advances have allowed scientists to start mapping brains in their entirety. In 1986, British researchers published the circuitry of a tiny worm, made up of 302 neurons. In subsequent years, researchers charted bigger brains, such as the 140,000 neurons in the brain of a fly.

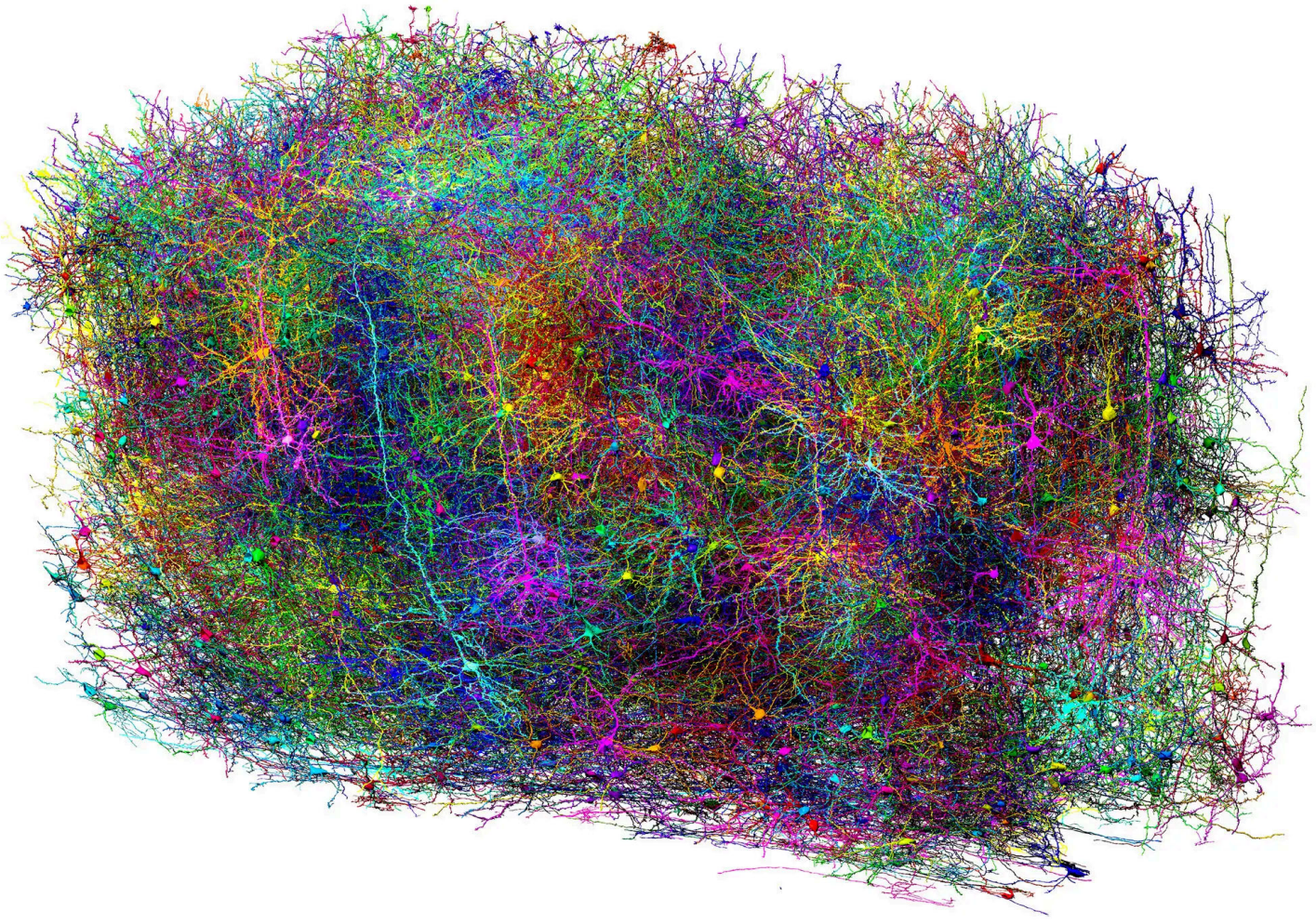
Could Dr. Crick's impossible dream be possible after all? In 2016, the American government began a $100 million effort to scan a cubic millimeter of a mouse brain. The project — called Machine Intelligence from Cortical Networks, or MICrONS — was led by scientists at the Allen Institute for Brain Science, Princeton University and Baylor College of Medicine.

The researchers zeroed in on a portion of the mouse brain that receives signals from the eyes and reconstructs what the animal sees. In the first stage of the research, the team recorded the activity of neurons in that region as it showed a mouse videos of

different landscapes.

The researchers then dissected the mouse brain and doused the cubic millimeter with hardening chemicals. Then they shaved off 28,000 slices from the block of tissue, capturing an image of each one. Computers were trained to recognize the outlines of cells in each slice and link the slices together into three-dimensional shapes. All told, the team charted 200,000 neurons and other types of brain cells, along with 523 million neural connections.

For Nuno da Costa, a biologist at the Allen Institute and one of the leaders of the project, just watching the cells take shape on his computer screen was breathtaking. “These neurons are absolutely stunning — it gives me pleasure,” he said.



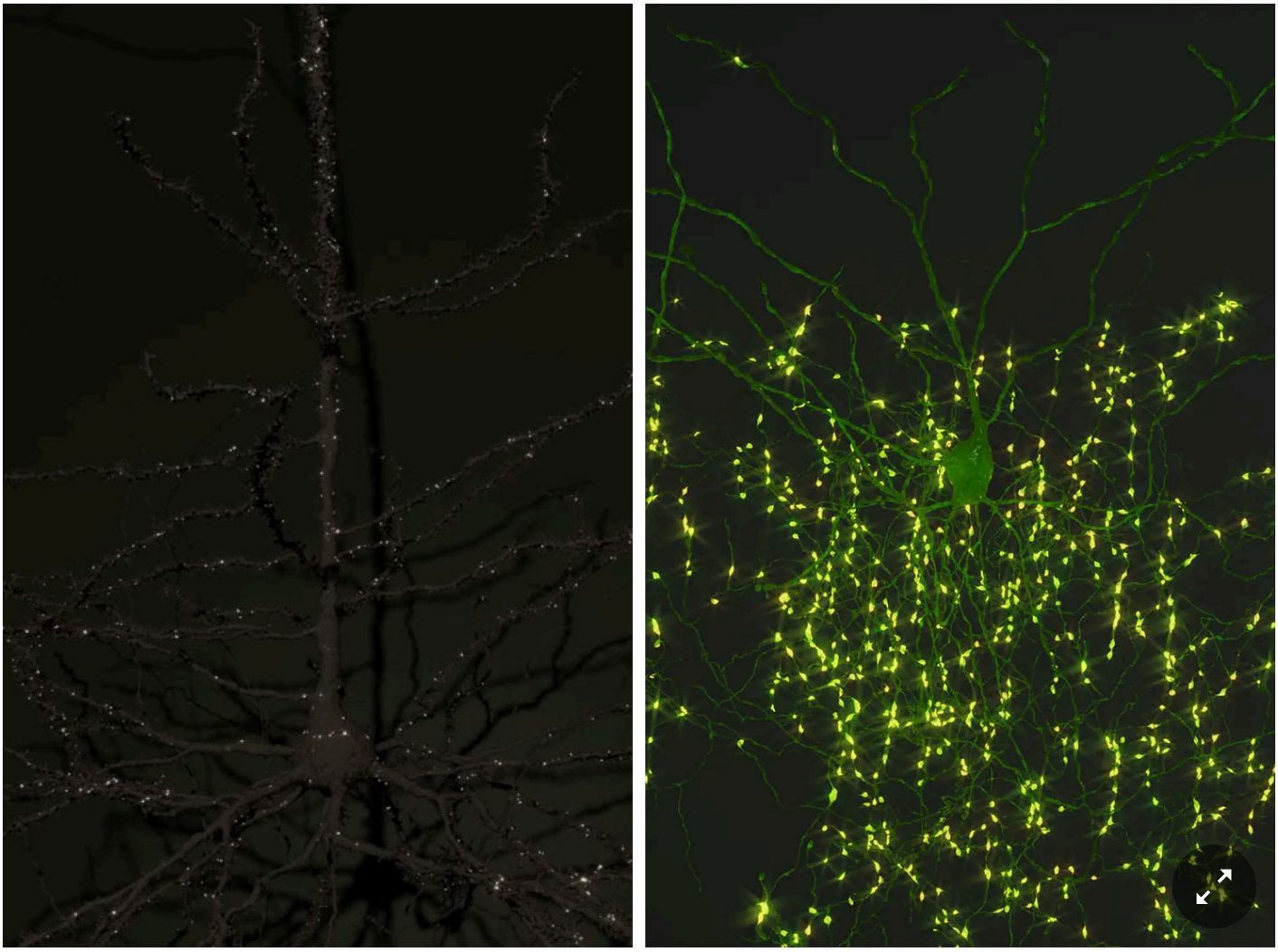
A small fraction of the neurons that were mapped in one cubic millimeter of mouse brain. Allen Institute

To understand how this mesh of neurons functioned, Dr. da Costa and his colleagues mapped the activity that had been recorded when the mouse looked at videos.

“Imagine that you come to a party that has 80,000 people, and you can be aware of every conversation, but you don’t know who is talking to whom,” Dr. da Costa said. “And now imagine that you have a way to know who is talking to whom, but you have no idea what they’re saying. If you have these two things, you can tell a better story about what’s happening at the party.”

Analyzing the data, the researchers discovered patterns in the wiring of the brain that had escaped notice until now. They identified distinct kinds of inhibitory neurons, for instance, that link only to certain other types of neurons.

“When you go into studying the brain, it seems kind of hopeless — there are just so many connections and so much complexity,” said Mariela Petkova, a biophysicist at Harvard who was not involved in the MICrONS project. “Finding wiring rules is a win. The brain is a lot less messy than people thought,” she said.



A single layer of neurons, left, with each input synapse denoted in white; and a “chandelier cell,” so named for the vertical arrangement of its axons.

Many of the MICrONS researchers are now pitching in on a bigger project: mapping an entire mouse's brain. With a volume of 500 cubic millimeters, a full brain would take decades or centuries to chart with current methods. The scientists will have to find additional tricks in order to finish the project in a decade.

"What they've already had to do to get here is heroic," said Gregory Jefferis, a neuroscientist at the University of Cambridge who was not involved in the MICrONS project. "But we've still got a mountain to climb."

Forrest Collman, a member of the MICrONS project at the Allen Institute, is optimistic. He and his colleagues recently discovered how to make microscopically thin sections from an entire mouse brain. "Some of these barriers are starting to fall," Dr. Collman said.

But our own brain, which is about a thousand times bigger than a mouse's, presents a much bigger challenge, he added. "The human brain right now feels like outside the range of what is possible," he said. "We are not going there anytime soon."

But Sebastian Seung, a neuroscientist at Princeton and a member of the MICrONS project, noted that mouse brains and human brains are similar enough that researchers might glean clues that could help them find medications to effectively treat psychological disorders without causing harmful side effects.

"Our current methods of manipulating the nervous system are incredibly blunt instruments," Dr. Seung said. "You put in a drug, and it goes everywhere," he added. "But being able to actually reach in and manipulate a cell type — that's precision."

The efforts to map a whole mouse brain are supported by funding from a long-running National Institutes of Health program called the BRAIN initiative. But the future of the endeavor is uncertain. Last year, Congress cut funding to the BRAIN initiative by 40 percent, and last month President Trump signed a bill cutting support by another 20 percent.

Dr. Bock noted that brain-mapping efforts like MICrONS take years, partly because they require the invention of new technologies and software along the way.

"We need consistency and predictability of science funding to realize these long-term goals," Dr. Bock said.