

"The brain is beautiful yet mysterious. Driven by innovative technologies and new approaches in the field of neuroscience, our understanding of the brain—and what it means to be human—is coming into sharper focus. And with this knowledge, we're starting to see promising treatments move into the clinic, offering new ways to treat diseases and improve brain health."

John Ngai, Ph.D.

Director, NIH BRAIN Initiative

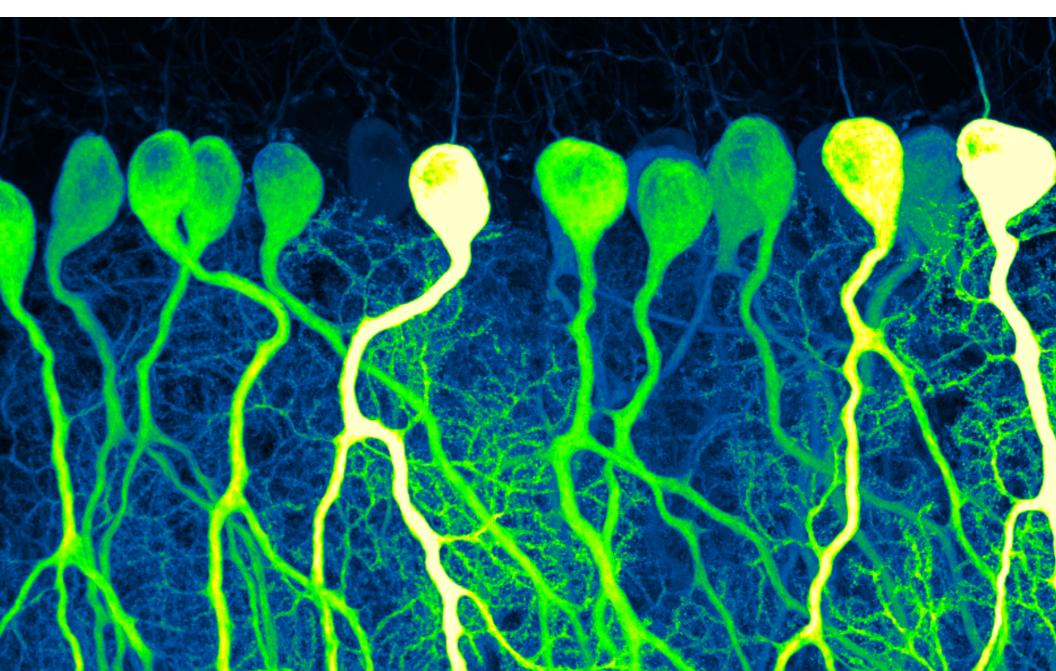
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Dark Commute at 4 a.m.

In the darkness of a confocal microscope room, bright fluorescent dyes reveal Purkinje cells winding their way through the tissue of the cerebellum. These complex, branching cells play roles in learning and memory. The cells in this photo, taken from sections of mouse

cerebellum, resemble pre-dawn commuters on the highways of the brain as they travel towards their eventual targets. *Credit: Silas Busch, The University of Chicago, Department of Neurobiology, Chicago, IL.*



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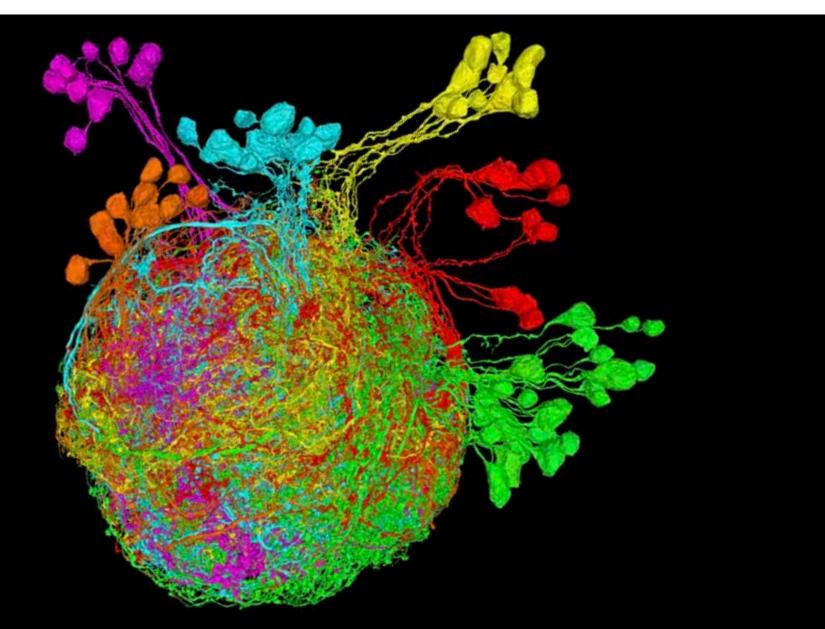
"We see human-like contours in these cells that are both literal and metaphorical signs of our exciting new experiments that are the first to directly compare the shape of mouse and human Purkinje cells."

Silas Busch

Shake a Leg

A reconstruction of premotor neurons controlling the fruit fly leg. Using an electron microscopy dataset of ultrathin sections of the Drosophila ventral nerve cord, researchers created a vivid display of the neural connections involved in fly leg movement. The structure of each neuron helps researchers determine their developmental lineages, represented by the different colors. This BRAIN-funded work represents the first comprehensive analysis

of a premotor connectome in any limbed animal and could eventually help scientists study neurological diseases that affect movement. *Credit: Andrew Cook, Jasper Phelps, Anthony Azevedo, Ellen Lesser, Leila Elabbady, Brandon Pratt, Wei-Chung Allen Lee, John Tuthill, University of Washington, Harvard Medical School/Tuthill and Lee Labs, Seattle, WA, Boston, MA.*



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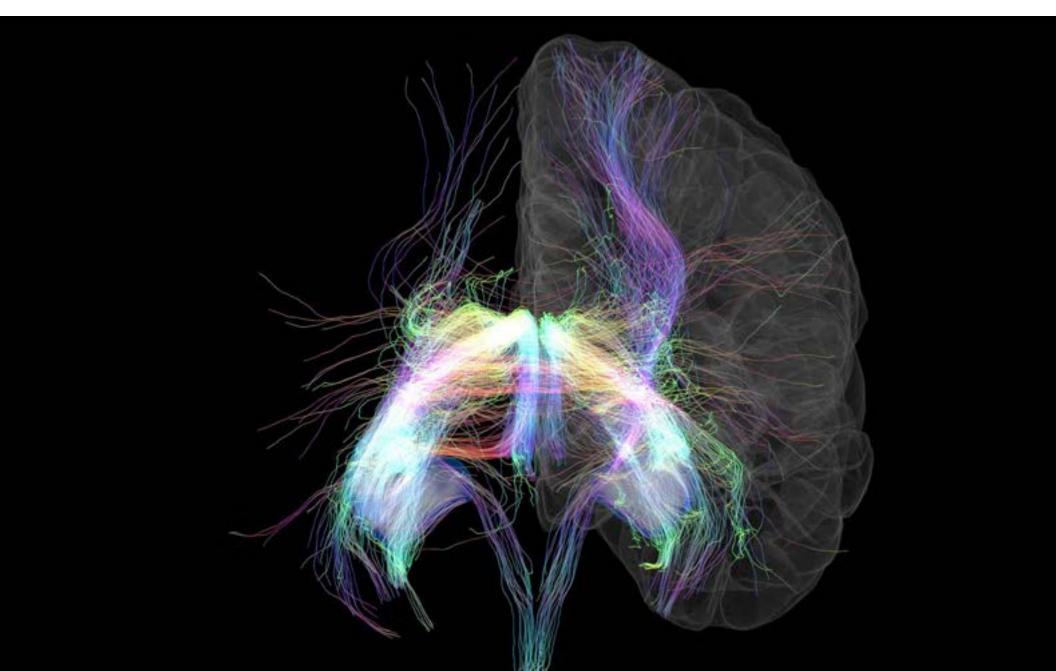
"Connectomics is a rapidly growing field of neuroscience that brings about endless possibilities for problem solving. The ability to map neural pathways and understand the developmental origin of these neurons provides an anatomical basis for established behaviors in animals."

Andrew Cook

Memory Lanes

The hippocampus is the brain's memory center. By combining two MRI scans, researchers can reveal the vast network of nerve fibers to and from the hippocampus—a wiring diagram for part of the brain. The axon fiber bundles are artificially colored depending on which direction they are head-

ing. For a better sense of just how immensely complex the brain's wiring is, this image represents less than 1% of the data collected. *Credit: Tyler Ard, USC Stevens Neuroimaging and Informatics Institute, Los Angeles, CA.*



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"We have developed incredible abilities to look at so much more than we can show through a simple image—it's truly an exciting time for research."

Brainbow Road

White matter fiber pathways of the human brain. They were reconstructed using diffusion MRI tractography, the only method for tracing neural connections in living humans. Tractography uses ultra high-resolution diffusion MRI data and computer modeling software to trace even the smallest connections, including short u-shaped fibers between adjacent gyri or ridges on the

brain's surface. Connections running between the left and right hemispheres are red, from back to front are green, and up and down are blue. Credit: Lauren J. O'Donnell, Yogesh Rathi, and Nikos Makris, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.



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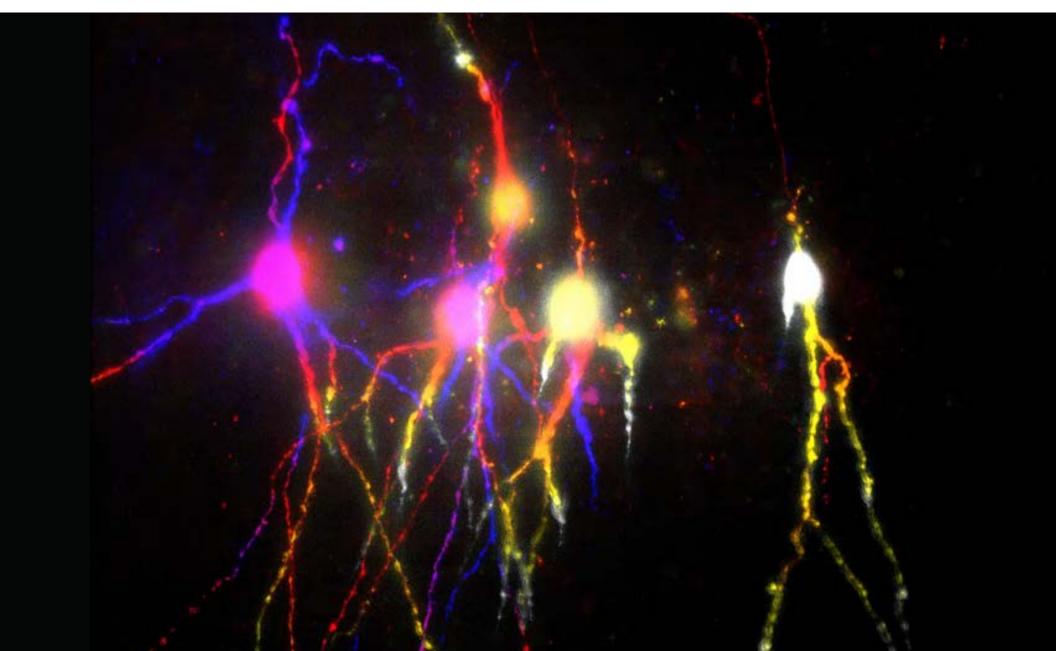
"Superficial white matter contains short connections that link nearby regions of the brain's cerebral cortex. These connections enable detailed, rich information processing between brain areas and are critical for human thought and behavior."

Lauren J. O'Donnell

The Dentate Disco

A dance of color reveals neurons called granule cells in epileptic human brain tissue. In a BRAIN-funded study, samples from the dentate gyrus were taken from patients undergoing surgery to treat epileptic seizures. Using patch-clamp electrophysiology, scientists recorded electrical activity of individual neurons and filled each neuron with a cellular tracer. They then

stained the neurons and used lasers to excite the fluorescent molecule. The resulting image represents a significant stride in the quest towards deciphering the mysteries of human neurons and circuits, as well as treating related disorders. *Credit: Tanvi Butola, NYU Grossman School of Medicine, New York City.*



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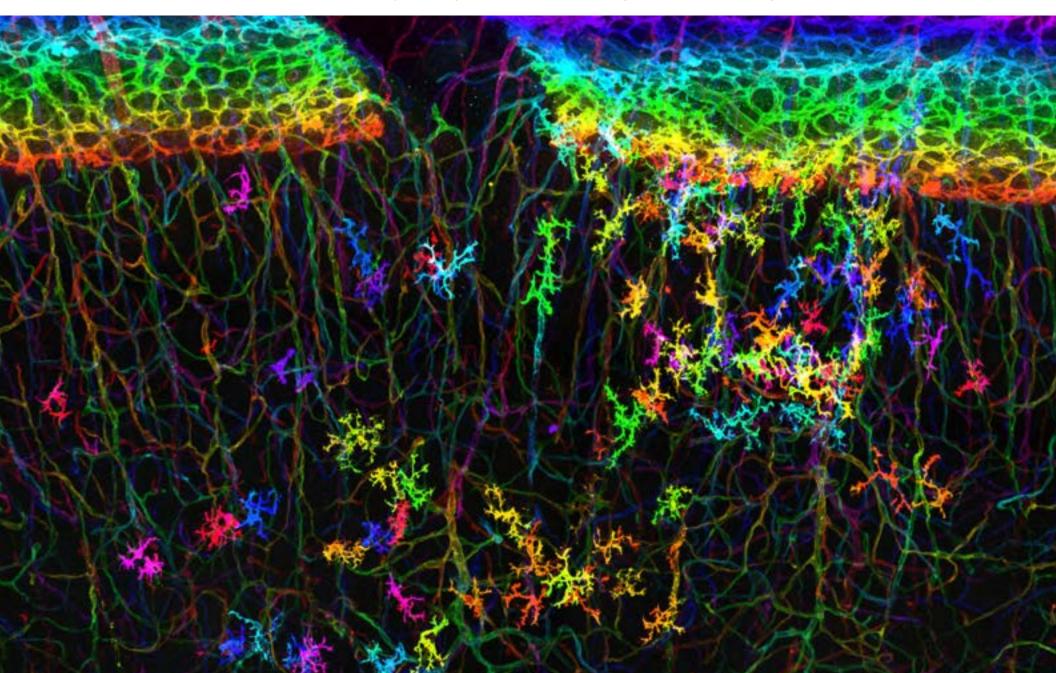
"Neuroscience stands as the ultimate frontier. We are slowly scaling this frontier, but much of our current understanding of the brain's structure and functions comes from animal models."

Tanvi Butola

Rainbow Microglia

Microglia intertwined with tiny blood vessels, called microvessels, in the primary somatosensory cortex of a 4-day-old mouse. Genetic labeling techniques and 3D imaging were used in this study to visualize a subset of these immune cells and vascular smooth muscle. This snapshot is part of a

BRAIN-funded project to build a common coordinate atlas of the developing mouse brain, allowing scientists to observe and quantify distinct cell types during neurodevelopment. *Credit: Josephine Liwang, Penn State College of Medicine, Yongsoo Kim lab, State College, PA.*



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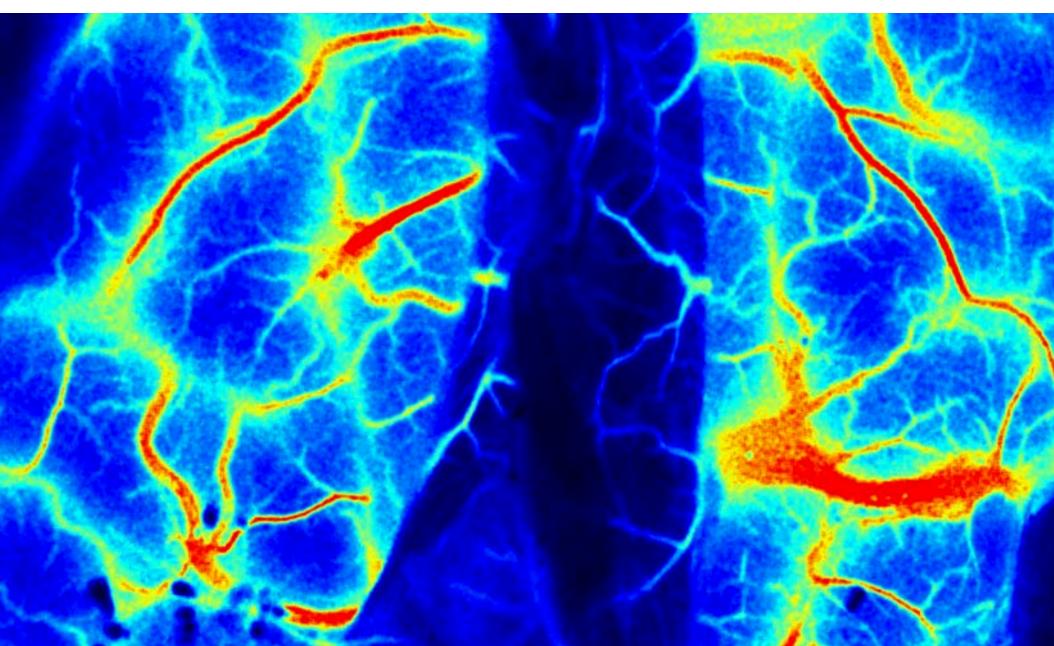
"This image demonstrates the incredible ability to visualize the morphologies of individual cells and blood vessels on a brain wide scale, providing insight into brain development."

Josephine Liwang

Cortical Blood Flow

This colorful image demonstrates blood flow on the cortex of a pig brain, visualized by a laser speckle imaging device. Red and blue represent high and low blood flow, respectively. Scientists can use porcine or pig models of stroke to assess neurophysiological and hemodynamic changes across the hemispheres, and at locations near or far from the stroke area. This will help

us better understand the pathophysiology behind stroke development and may lead to new treatment approaches that target the brain's microcirculation system. *Credit: Sourav Patnaik, Aksharkumar Dobariya, Juan Pascual, and Ulrike Hoffmann, The University of Texas Southwestern Medical Center, Dallas, TX.*



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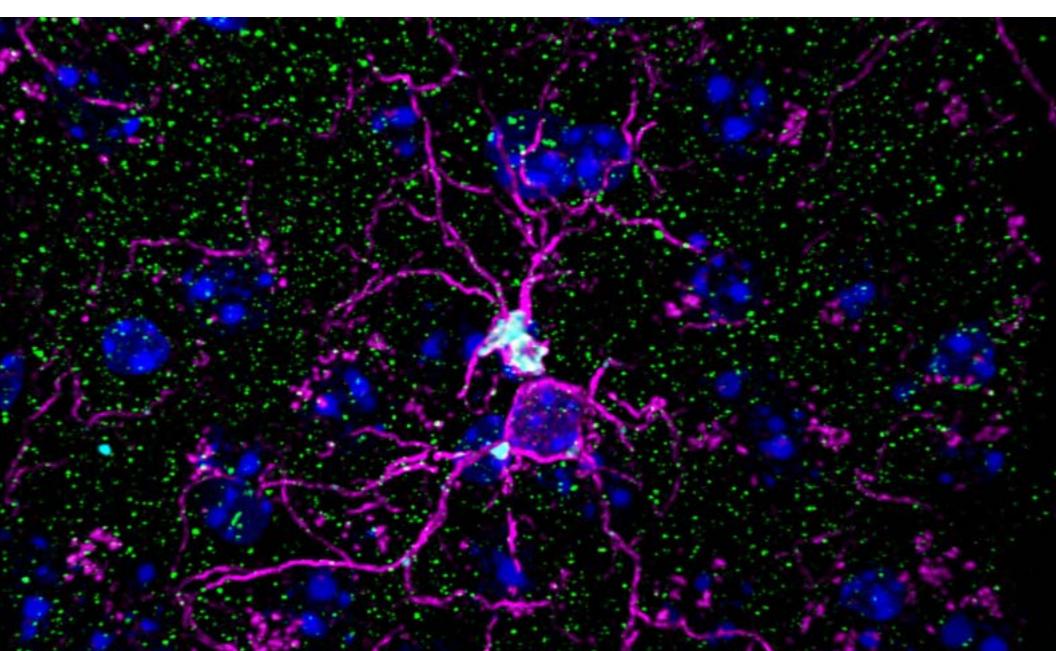
"This photo represents quite simply the complex architecture of the blood vessels in the brain."

Sourav Patnaik

Caught in the Act

This image shows microglia (magenta), a type of immune cell found in the brain, digesting nerve terminal cells (green). The digestive compartment of the microglia is shown in cyan. Microglia normally act as housekeepers, pruning synapses and cleaning away debris so that new connections between neurons can be refined. This ensures that the brain remains

healthy and functioning correctly. However, if left unchecked, overactive microglia can cause neuronal loss and neurodegenerative diseases. Here, scientists are studying how genetic mutations can lead to this toxic process in mouse models of Parkinson's disease. *Credit: Mengfei Bu, Lab of Matthew Farrer, Department of Neurology, University of Florida, Gainesville, FL.*



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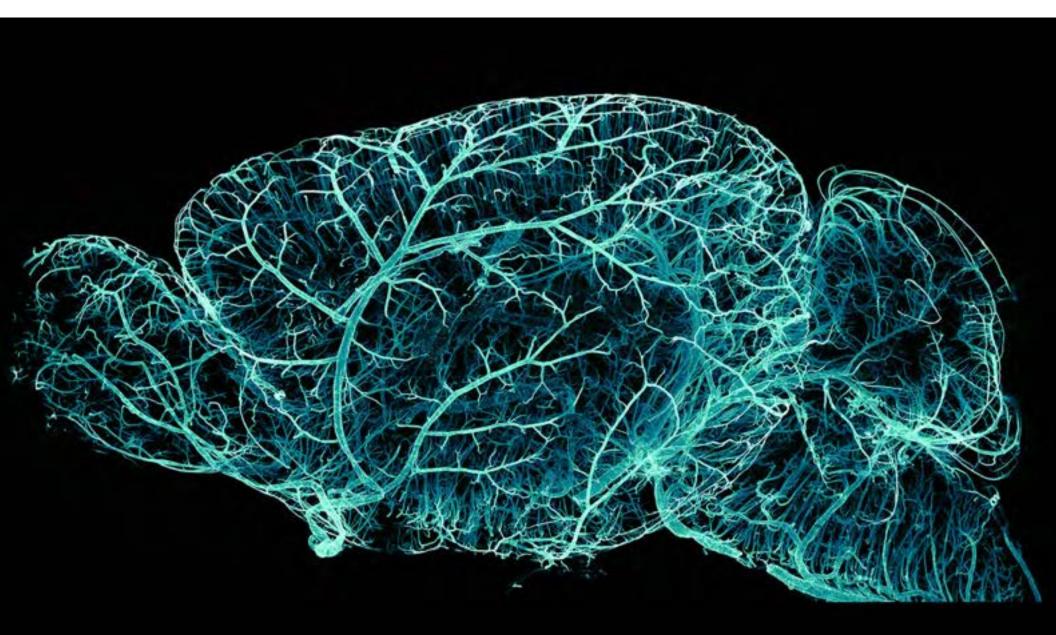
"To me it highlights microglia's hard work behind the scenes—surveying the brain, clearing debris, and pruning unwanted synapse so that neurons could perform their best."

Mengfei Bu

Arteries: A Brain Imaged With Heart

This image shows a mouse brain stained for smooth muscle cells surrounding arteries using tissue-clearing and immunolabeling methods. A team of scientists and engineers at Translucence Biosystems developed a technique to render large, intact tissues optically clear, allowing them to image whole

brains in 3D instead of cutting the tissue into thin slices and imaging each one-by-one. This helps scientists visualize the blood-brain barrier, a critical barricade that limits the entry of therapeutics into the brain. *Credit: Translucence Biosystems, Irvine, CA.*



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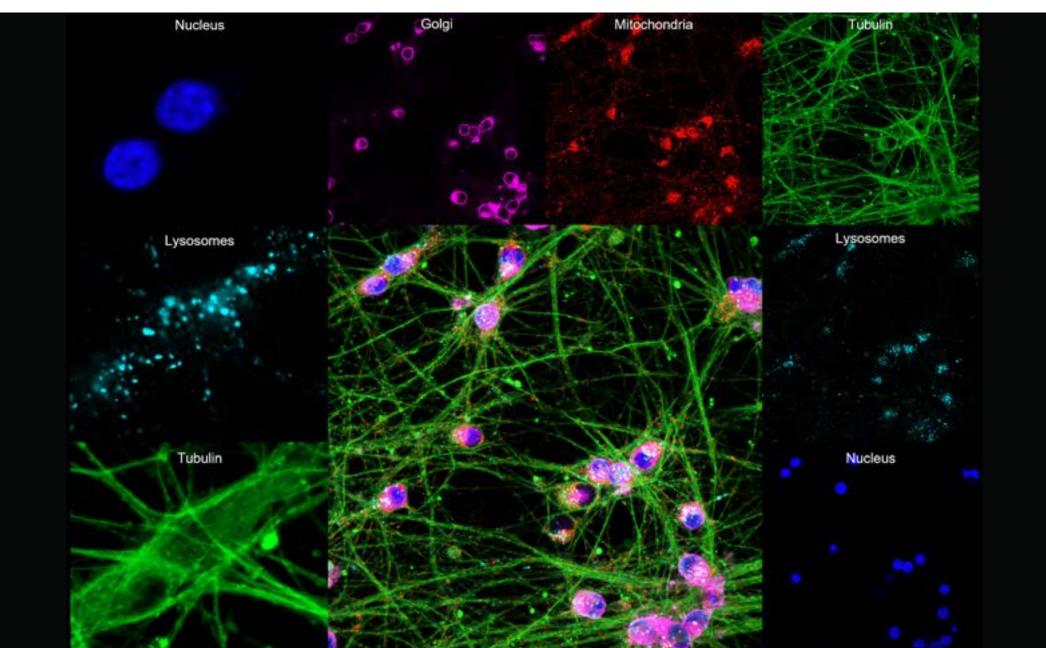
"This image, which shows arteries throughout the brain, provides a simple encapsulation of the power of tissue clearing techniques that allow for high resolution imaging of the intact brain and other organs."

Damian Wheeler

The Galaxy Within iNeurons

With modern technology, cells collected from healthy donors can be reprogrammed into cortical neurons, called iNeurons. These cells carry identical genetic information as their donor cells, allowing scientists to understand which genes cause a disease and how they contribute to disease risk. This marks a major step towards identifying new therapeutic targets for Alzhei-

mer's and other neurodegenerative diseases. *Credit: Marianita Santiana, Erika Lara, Daniel Ramos, Andy Qi, Caroline Pantazis, Julia Stadler, Michael Ward, and Mark Cookson, iPSC Neurodegenerative Disease Initiative, Center for Alzheimer's and Related Dementias, National Institute of Neurological Disorders and Stroke, Bethesda, MD.*



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"Targeting different cellular pathways, organelles, and structures from iNeurons will provide the scientific community with the right tools and the perfect opportunity to understand the cellular mechanisms associated with these diseases."

Marianita Santiana

High Above the Rivers of the Brain

A newly developed technique called functional ultrasound localization microscopy (fULM) combined with 3D animation software allows for the visualization of blood vessels deep within the brain. Scientists are working on improving this method to record the entire vasculature of the human

brain and other organs, which would provide a window into the activity occurring within these tissues. *Credit: Alexandre Dizeux, Physics for Medicine Paris, Paris, France.*



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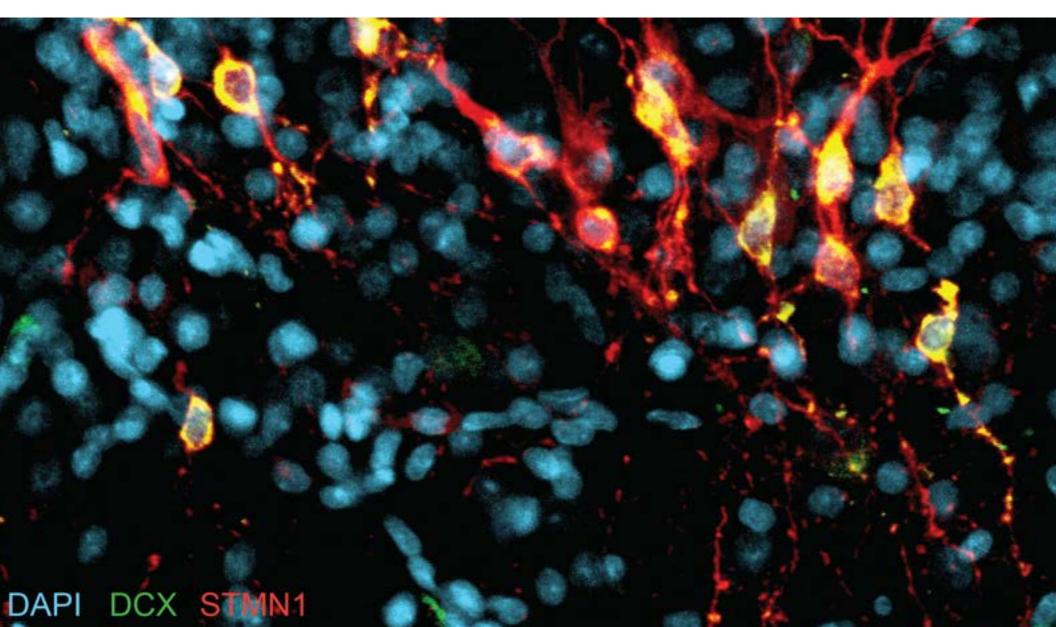
"This imaging technique gives us access to information like blood flow and speed and vessel diameter changes, allowing us to measure neural activity in deep regions of the brain."

Alexandre Dizeux

Neurons De Novo

Seen here in yellow are newly produced neurons, chiefly, immature dentate granule neurons, found in brain samples from infancy to age 92. Researchers used state-of-the-art single cell RNA-sequencing and machine learning analysis to identify novel neuronal molecular markers for these cells, such as STMN1. The study involved measuring the expression of over 20,000 genes, cell-by-cell in tissue samples from different age groups. This discovery is

evidence of neurogenesis, or the birth of new neurons, in the hippocampus across the lifespan. The brain region is critical for learning, memory, and mood regulation. Scientists have long debated whether the human brain can produce new neurons as we age. *Credit: Yi Zhou, University of Pennsylvania, Philadelphia, PA.*



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"This project taught us that cells, like humans, have diverse populations. Therefore, to accurately determine a cell's identity, it is necessary to capture a comprehensive picture of gene expression within a cell."

Yi Zhou

