An ultra detailed map of the brain region that controls movement, from mice to monkeys to humans

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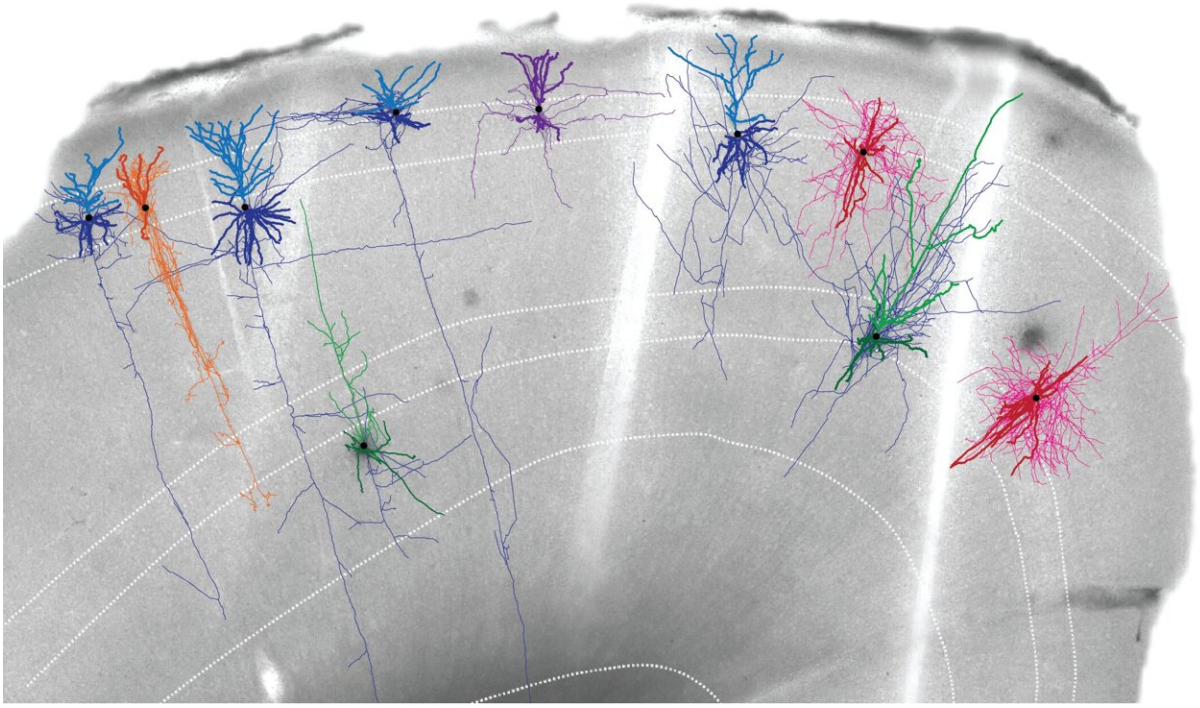


Digital reconstructions of human neurons overlaid on a slice of brain tissue donated by a brain surgery patient. Allen Institute researchers are able to capture electrical information from these live human neurons, as well as their 3D shape and gene expression, through a technique known as Patch-seq. This image shows several different types of human neurons in the medial temporal gyrus of the neocortex, the outermost shell of the mammalian brain. Credit: Allen Institute

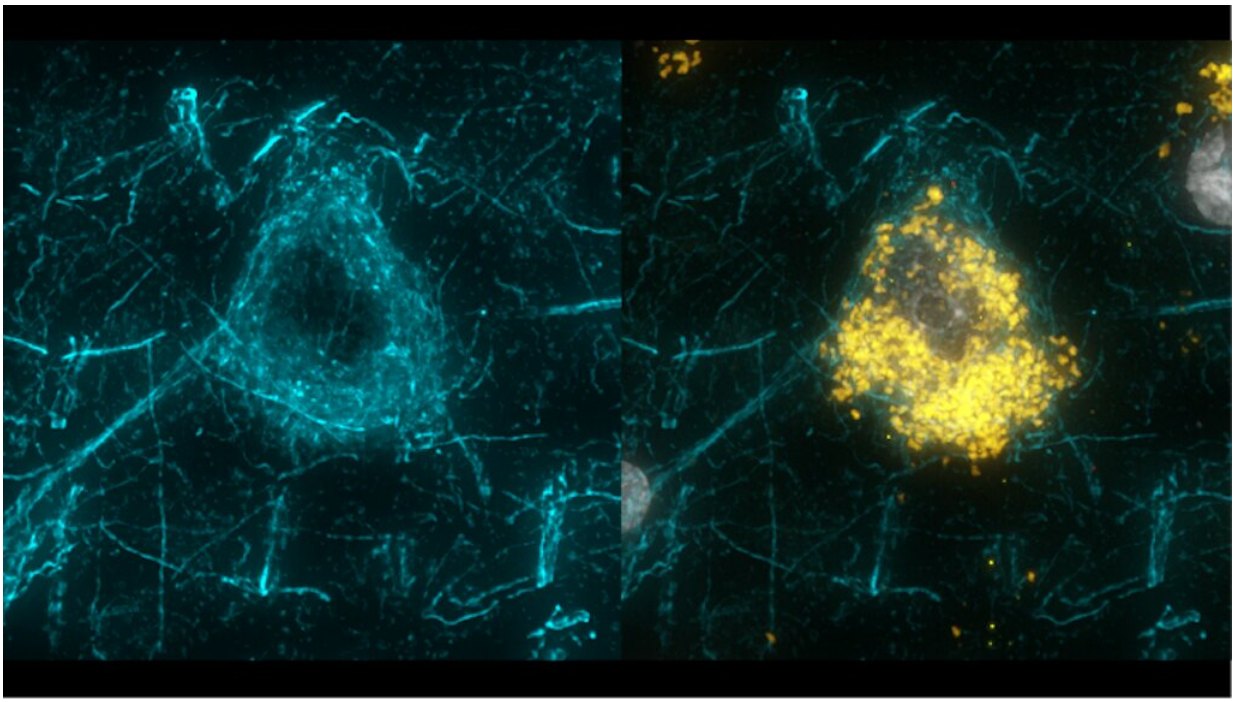
Before you read any further, bring your hand to your forehead.

It probably didn't feel like much, but that simple kind of motion required the concerted effort of millions of different neurons in several regions of your brain, followed by signals sent at 200 mph from your brain to your spinal cord and then to the muscles that contracted to move your arm.

At the cellular level, that quick motion is a highly complicated process and, like most things that involve the human brain, scientists don't fully understand how it all comes together.

Now, for the first time, the neurons and other cells involved in a region of the human, mouse and monkey brains that controls movement have been mapped in exquisite detail. Its creators, a large consortium of neuroscientists brought together by the National Institutes of Health's Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, say this brain atlas will pave the way for mapping the entire mammalian brain as well as better understanding mysterious brain diseases—including those that attack the neurons that control movement, like amyotrophic lateral sclerosis, or ALS.

The atlas is described in a special package of 17 articles published today in the journal *Nature*, including a single flagship paper that describes the entire atlas.



Scientists at the Allen Institute are studying human neurons that appear to be highly specialized as compared to their rodent counterparts. One of these newly described neuron types, the CARM1P1 neuron, sends long-range connections in the brain and may be selectively vulnerable in Alzheimer's disease. Credit: Allen Institute

"In a human brain, there are more than 160 billion cells. Our brain has more than 20 times more cells than there are people in this world," said Hongkui Zeng, Ph.D., Executive Vice President and Director of the Allen Institute for Brain Science, a division of the Allen Institute, and lead investigator on several BRAIN Initiative-funded studies. "To understand how a system works, you need to first build a parts list. Then you have to understand what each part is doing and put the pieces together to understand how the whole system works. That's what we're doing with the brain."

The massive BRAIN Initiative-funded collaboration involved dozens of research teams around the country who worked together to complete a cell-by-cell atlas of the primary motor cortex, a part of the mammalian brain that controls movement. Combining more than a dozen different techniques to define brain "cell types" across three different species of mammals, the resulting open-access data collection is by far the most comprehensive and detailed map of any part of the mammalian brain ever released. The researchers classified the millions of neurons and other kinds of brain cells present in the motor cortex into many different cell-type categories—the actual number of different brain cell types in this region depends on how they are being measured, but ranges from several dozen to more than 100.

The researchers picked the primary motor cortex in part because it's similar across all mammalian species—while humans, monkeys and mice have many differences between our brains, the way we control movement is very similar—and because it's representative of the neocortex, the outermost shell of the mammalian brain that not only integrates sensory and motor information but also gives rise to our complex cognitive functions. This completed atlas is one large step in the effort to create a catalog or census of all brain cell types through the BRAIN Initiative Cell Census Network, or BICCN. The NIH launched the BICCN in 2017, awarding nine collaborative network grants, three of which are led by Allen Institute for Brain Science researchers.

Like a population census, the cell census aims to catalog all different types of brain cells, their properties, their relative proportions and their physical addresses to get a picture of the cell populations that together form our brains. Knowing the "normal" brain's cellular makeup is a key step to understanding what goes wrong in disease.

"If we really want to understand how the brain works, we have to get down to its fundamental unit. And that is the cell," said Ed Lein, Ph.D.,

Senior Investigator at the Allen Institute for Brain Science and lead investigator on several BRAIN Initiative studies focused on the human brain. "This is also clinically important because cells are the locus of disease. By understanding which cells are vulnerable in different brain diseases, we can better understand and ultimately treat the diseases themselves. The hope with these studies is that by making this fundamental classification of cell types, we can lay the groundwork for understanding the cellular basis of disease."

The atlas's creators used several different methods to measure a variety of cellular properties to define a cell type by correlating and integrating these properties, which include the complete set of genes a cell switches on; a cell's "epigenetic" landscape, which defines how genes are regulated; cells' 3D shapes; their electrical properties; and how they connect to other cells. The single-cell gene expression and epigenetic data were especially important as the researchers were able to use these data to integrate all the other kinds of cell-type data, creating a common framework to classify cell types and compare them within and between species.

The studies required not only collaboration among researchers to design and execute the experiments, but also coordination and public sharing of the data that resulted from the atlas project and other projects under the BICCN. The Brain Cell Data Center, or BCDC, is headquartered at the Allen Institute. The data center, led by Allen Institute for Brain Science Investigator Michael Hawrylycz, Ph.D., helps to organize the BICCN consortium and provides a single point of access to the study's data-archiving centers across the country.

"One of our many limitations in developing effective therapies for human brain disorders is that we just don't know enough about which cells and connections are being affected by a particular disease, and therefore can't pinpoint with precision what and where we need to

target," said John Ngai, Ph.D., Director of the NIH BRAIN Initiative. "The Allen Institute has played an important role in coordinating the large amounts of data produced by the BRAIN cell census project that provide detailed information about the types of cells that make up the brain and their properties. This information will ultimately enable the development of new therapies for neurologic and neuropsychiatric diseases."

Scientists at the Allen Institute for Brain Science played a role in nine of the 17 published studies and led or co-led six of them. The four primary Allen Institute-led studies explored:

- How cell types in the primary motor cortex compare across mice, humans and marmoset monkeys. The research team found that most motor cortex brain cell types have similar counterparts across all three species, with species-specific differences at the level of proportions of cells, their shapes and electrical properties, and individual genes that are switched on and off. For example, humans have about twice as many excitatory neurons as inhibitory neurons in this region of the brain, while mice have five times as many. The researchers also delved into the famous Betz cells, enormous neurons that project to the spinal cord that exist in us, monkeys and many other larger mammals, and captured the first known electrical recordings from human Betz cells, which degenerate in ALS. Mice have evolutionarily related neurons based on shared genetic programs, but their shapes and electrical properties are very different from those in humans.
- A broader analysis of brain cell types in the human brain, looking at the second and third layers of the 6-layered neocortex. These layers, and the neocortex overall, are much larger and contain a larger diversity of cells in humans and other primates as compared to rodents. Allen Institute researchers used a three-prong technique known as Patch-seq to measure the electrical

properties, genes and the 3D shapes of several kinds of neurons in these layers in tissue samples donated by brain surgery patients. The study characterizes these neurons in living human tissues and demonstrates an increased diversity of the types of neurons specialized to communicate between different regions of the human cortex, including delving into a specialized type of human neuron that is especially vulnerable in Alzheimer's disease.

- The largest collection to date of complete brain-wide reconstructions of more than 1,700 different neurons in the mouse brain. This form of 3D neuron-tracing is extensive and complicated due to the cells' lengthy and delicate axons and dendrites, but it yields important information about the long-distance connections different neuron types make through their axon arbors reaching faraway brain regions. Allen Institute researchers find that these neurons' axon arbors show extremely diverse patterns, some with just a few focused branches while others spread across large areas. For example, some neurons in the structure known as the claustrum send axon arbors in a crown-like fashion around the entire circumference of the neocortex. Characteristic connection patterns like these are a critical attribute used to help classify a brain cell type.
- The cellular makeup of the mouse primary motor cortex, sorting approximately 500,000 neurons and other brain cells into cell-type categories based on the suite of genes each cell switches on (the "transcriptome") as well as the gene-regulatory modifications on a cell's chromosomes (the "epigenome"). Using a range of techniques, Allen Institute researchers and their collaborators generated seven types of transcriptomic and two types of epigenomic datasets, then developed computational and statistical methods to integrate these datasets into shared "evolutionary tree" of cell types. The study led to the discovery of thousands of marker genes and other DNA sequences specific

for each of these cell types.

More information: Neuroscience: Mapping the mammalian motor cortex, *Nature* (2021). DOI: 10.1038/s41586-021-03950-0

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