A new era in brain science: Researchers unveil human brain cell atlas

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A diagram demonstrating how "barCodes" ("scMCodes") can be used to identify and classify cell types in the brain. The image shows an anatomical brain cross section, an abstraction of the brain with regions represented as colored circles (blue, red, green, and yellow), and a barcode to represent the technique used by the scientists. Credit: Salk Institute

Salk Institute researchers, as part of a larger collaboration with research teams around the world, analyzed more than half a million brain cells from three human brains to assemble an atlas of hundreds of cell types that make up a human brain in unprecedented detail.

The research, published in a special issue of the journal *Science* on October 13, 2023, is the first time that techniques to identify brain cell subtypes originally developed and applied in mice have been applied to human brains.

"These papers represent the first tests of whether these approaches can work in human brain samples, and we were excited at just how well they translated," says Professor Joseph Ecker, director of Salk's Genomic Analysis Laboratory and a Howard Hughes Medical Institute investigator. "This is really the beginning of a new era in brain science, where we will be able to better understand how brains develop, age, and are affected by disease."

The new work is part of the National Institute of Health's Brain Research Through Advancing Innovative Neurotechnologies Initiative, or The BRAIN Initiative, an effort launched in 2014 to describe the full plethora of cells—as characterized by many different techniques—in mammalian brains. Salk is one of three institutions awarded grants to act as central players in generating data for the NIH BRAIN Initiative Cell Census Network, BICCN.

Every cell in a human brain contains the same sequence of DNA, but in different cell types different genes are copied onto strands of RNA for use as protein blueprints. This ultimate variation in which proteins are found in which cells—and at what levels—allows the vast diversity in types of brain cells and the complexity of the brain. Knowing which cells rely on which DNA sequences to function is critical not only to understanding how the brain works, but also how mutations in DNA can

cause brain disorders and, relatedly, how to treat those disorders.

"Once we scale up our techniques to a large number of brains, we can start to tackle questions that we haven't been able to in the past," says Margarita Behrens, a research professor in Salk's Computational Neurobiology Laboratory and a co-principal investigator of the new work.

In 2020, Ecker and Behrens led the Salk team that profiled 161 types of cells in the mouse brain, based on methyl chemical markers along DNA that specify when genes are turned on or off. This kind of DNA regulation, called methylation, is one level of cellular identity.

In the new paper, the researchers used the same tools to determine the methylation patterns of DNA in more than 500,000 brain cells from 46 regions in the brains of three healthy adult male organ donors. While mouse brains are largely the same from animal to animal, and contain about 80 million neurons, human brains vary much more and contain about 80 billion neurons.

"It's a big jump from mice to humans and also introduces some technical challenges that we had to overcome," says Behrens. "But we were able to adapt things that we had figured out in mice and still get very high quality results with human brains."

An abstract representation of cell diversity in the brain. Individual nuclei are colored in the bright hues of t-SNE plots used in epigenomics analysis to distinguish individual brain cell types. Layers of background color represent the local environmental factors of each brain region that influence cell function. Credit: Michael Nunn

At the same time, the researchers also used a second technique, which analyzed the three-dimensional structure of DNA molecules in each cell to get additional information about what DNA sequences are being actively used. Areas of DNA that are exposed are more likely to be accessed by cells than stretches of DNA that are tightly folded up.

"This is the first time we've looked at these dynamic genome structures at a whole new level of cell type granularity in the brain, and how those

structures may regulate which genes are active in which cell types," says Jingtian Zhou, co-first author of the new paper and a postdoctoral researcher in Ecker's lab.

Other research teams whose work is also published in the special issue of *Science* used cells from the same three human brains to test their own cell profiling techniques, including a group at UC San Diego led by Bing Ren—also a co-author in Ecker and Behrens' study. Ren's team revealed a link between specific brain cell types and neuropsychiatric disorders, including schizophrenia, bipolar disorder, Alzheimer's disease, and major depression. Additionally, the team developed artificial intelligence deep learning models that predict risk for these disorders.

Other groups in the global collaboration focused on measuring levels of RNA to group cells together into subtypes. The groups found a high level of correspondence in each brain region between which genes were activated, based on the DNA studies by Ecker and Behrens' team, and which genes were found to be transcribed into RNA.

Since the new Salk research was intended as a pilot study to test the efficacy of the techniques in human brains, the researchers say they can't yet draw conclusions about how many cell types they might uncover in the human brain or how those types differ between mice and humans.

"The potential to find unique cell types in humans that we don't see in mice is really exciting," says Wei Tian, co-first author of the new paper and a staff scientist in Ecker's lab. "We've made amazing progress but there are always more questions to ask."

In 2022, the NIH Brain Initiative launched a new BRAIN Initiative Cell Atlas Network (BICAN), which will follow up the BICCN efforts. At Salk, a new Center for Multiomic Human Brain Cell Atlas aims to study cells from over a dozen human brains and ask questions about how the

brain changes during development, over people's lifespans, and with disease.

That more detailed work on a larger number of brains, Ecker says, will pave the way toward a better understanding of how certain brain cell types go awry in brain disorders and diseases.

"We want to have a full understanding of the brain across the lifespan so that we can pinpoint exactly when, how, and in which cell types things go wrong with disease—and potentially prevent or reverse those harmful changes," says Ecker.

More information: Wei Tian et al, Single-cell DNA methylation and 3D genome architecture in the human brain, *Science* (2023). DOI: 10.1126/science.adf5357.
www.science.org/doi/10.1126/science.adf5357

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