NEWS

Charting one cell at a time, scientists reveal brain's vast diversity

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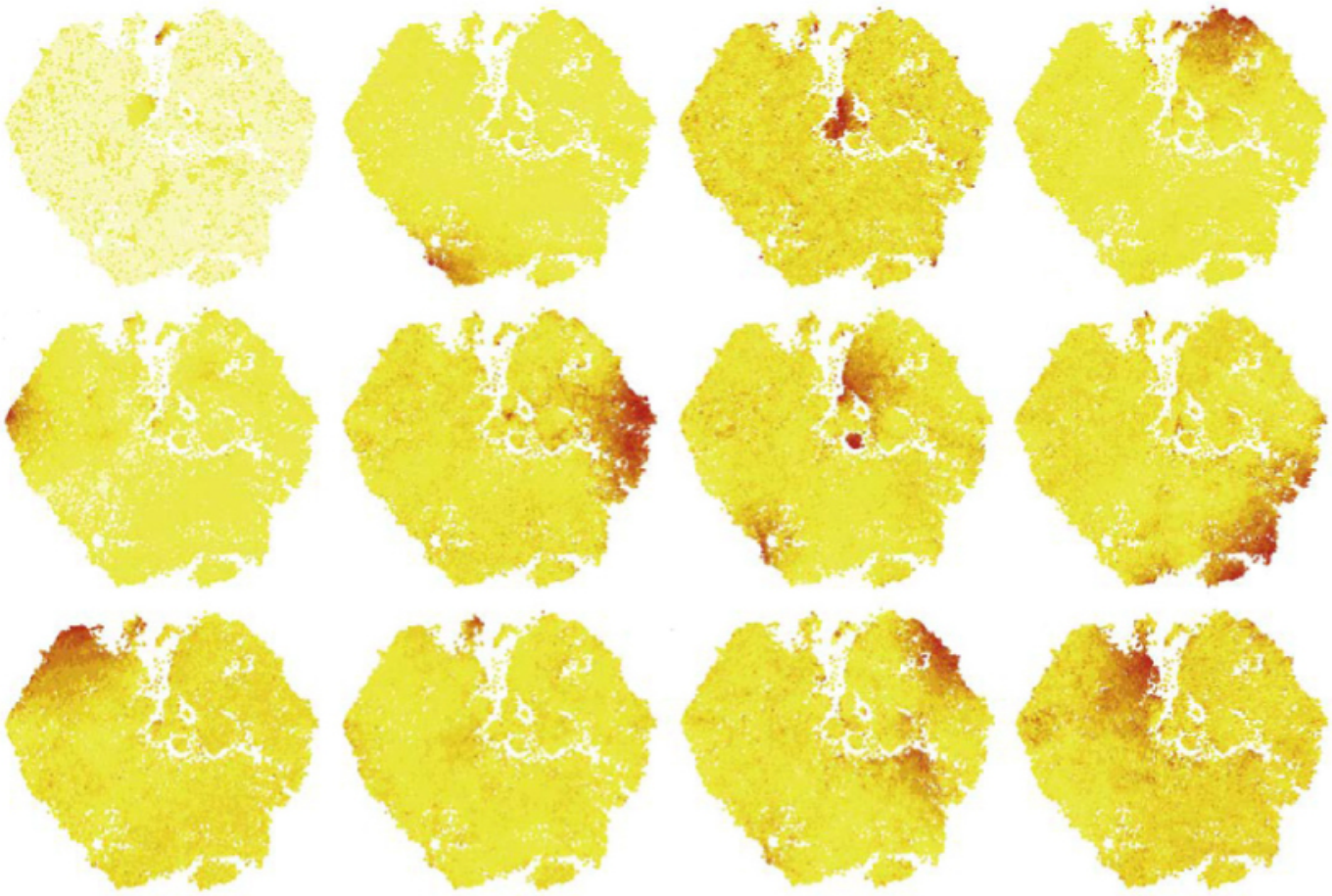

How many cell types exist in the brain? Two new mouse studies bring scientists a step closer to the answer[1,2].

The exact number is still elusive, but the studies define hundreds of cell types, including dozens that were previously unknown.

The work “provides a real blueprint for the diversity of cell types that exist in the brain,” says **Tomasz Nowakowski**, assistant professor of anatomy at the University of California, San Francisco, who was not involved in the studies. It solves what has “been a problem for over 100 years.”

Because of limitations in techniques, researchers have typically defined cell types by their function or shape, but the criteria used are inconsistent. In the new studies, by contrast, researchers used cutting-edge methods that enable them to sequence RNA **from one cell at a time**.

The findings may help scientists understand how brain cells are altered in conditions such as autism.

Both teams analyzed patterns of gene expression in hundreds of thousands of cells in the mouse brain. The data are available in two databases — **DropViz** and **MouseBrain.org** — that researchers can search by cell type or gene.

“These gene expression profiles of most cell types in the brain are extraordinarily valuable to neuroscientists,” says **Jason Stein**, assistant professor of genetics at the University of North Carolina at Chapel Hill, who was not involved in the studies. “They show us new, important and previously unknown components to the organ we study every day.”

One by one:

One team looked at 690,207 cells sampled from nine regions of an adult mouse brain. The other analyzed 492,949 cells in an adolescent mouse brain and parts of its peripheral nervous system. Both studies were published 9 August in *Cell*.

“Sequencing so many cells allows the identification of rare cell types, because you have to observe the cell type multiple times in order to be confident that it exists,” Stein says.

Each team used statistical methods to define categories of cells based on similarities in gene expression.

For example, one team, led by **Steve McCarroll** identified 11 basic cell groups, such as **microglia**, or neurons that release the chemical messenger glutamate. They then analyzed each group to find 565 distinct types of cells.

“What we know about cell types is really important foundational knowledge,” says McCarroll, professor of biomedical sciences and genetics at Harvard University. The findings “allow you to

think about each cell population in the context of all other cell populations."

The team found, for example, that the glutamatergic neurons are specialized to regions of the cortex more than any other type of neuron.

This finding "goes against the long-standing view that the cerebral cortex is a uniform sheet-like structure that is identical no matter where you look," Nowakowski says.

Uncharted territory:

The other team, led by **Sten Linnarsson**, discovered seven distinct types of **astrocytes**, star-shaped brain cells that support neurons. Each type tends to cluster in a particular brain region.

Linnarsson's team also discovered rare cell types in the membranes surrounding the brain or blood vessels. And they found diverse cell types in understudied brain regions, such as the dorsal midbrain, which helps orient the body in relation to visual and auditory signals.

"Since we did [our study] systematically, we found many obscure cell types that nobody has ever focused on before," says Linnarsson, professor of molecular systems biology at the Karolinska Institute in Stockholm.

This cellular panorama of the brain may be especially valuable to autism researchers, who have tended to focus on specific regions, says Nowakowski.

The databases might reveal, for example, that an autism gene is important in an unexpected region. Or they might help researchers analyze multiple autism genes at once to see whether they cluster in certain cell types. Researchers could also use the data as a reference against which to compare cells from autism mice or from individuals with the condition.

Both teams aim to analyze gene expression in brain cells at various developmental stages. They also plan to chart cell types in postmortem brain tissue.

REFERENCES:

1. Saunders A. *et al. Cell* **174**, 1015-1030 (2018) **PubMed**
2. Zeisel A. *et al. Cell* **174**, 999-1014 (2018) **PubMed**