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Using genes to understand the brain's building blocks

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Credit: Human Brain Project

Understanding the cellular building blocks of the brain, including the number and diversity of cell types, is a fundamental step toward understanding brain function. Researchers at the Allen Institute for Brain Science have created a detailed taxonomy of cells in the mouse visual cortex based on single-cell gene expression, identifying 49 distinct cell types in the largest collection of individual adult cortical neurons characterized by gene expression published to date. The work appears this month online in *Nature Neuroscience*.

"Studying any system requires knowing what the system is made of," says Bosiljka Tasic, Ph.D., Assistant Investigator at the Allen Institute for Brain Science. "There are many ways to define the brain's cellular building blocks. Our approach was to look at all the genes that are expressed in individual cells in the mouse visual cortex and use that information to classify the cells."

The team developed a technique to isolate single cells from the adult mouse brain, and then obtained genome-wide gene expression data from these individual cells. Each cell expresses thousands of genes, making the cell classification problem an enormous computational task.

"Initially, the problem of classifying cells is like sorting Skittles in the dark," says Vilas Menon, Scientist II at the Allen Institute for Brain Science. "With single-cell gene expression data, we get the equivalent of color, or type, information, but we still have to extract it from the large-scale data set. Ultimately, we wanted to figure out how many types there were in an unbiased, data-driven way."

Tasic, Menon and their team used computational dimension reduction techniques, which collapse genes with similar expression patterns into gene sets. When single cells were analyzed by clustering in this lower-dimensional space, 49 distinct groups appeared based on unique combinations of genes they express, including 42 neuronal cell types and 7 non-neuronal types.

"Our human cortex is what gives rise to our unique thoughts and perceptions," says Christof Koch, Ph.D., President and Chief Scientific Officer at the Allen Institute for Brain Science. "Having this kind of objective analysis of cell types in this region of the brain is a basic piece of understanding we need, and provides a baseline for looking at other regions of the mouse brain and also at the human brain."

The data from this single cell analysis approach agree with and complement the Allen Brain Atlas: a brain-wide gene expression atlas of the mouse brain.

"Our unit of analysis was a single cell and all genes within each cell, but in our process, we lost fine spatial information," says Tasic. "But then, we were able to use our Allen Brain Atlas, which has brain-wide analysis of each gene, one gene at a time at cellular resolution, to more precisely locate each cell type. Our work is one more step toward assigning genes to specific cell types and then helping investigate what these genes do, how they work together, and how they ultimately make our nervous systems and us who we are."

"Categorizing the cells in visual cortex into these distinct types that are marked by specific genes will enable us to begin to understand what these cells and types do in the brain," says Hongkui Zeng, Ph.D., Investigator of Cell and Circuit Genetics at the Allen Institute for Brain Science. "Next, we can investigate how gene expression correlates with the anatomical, physiological and functional properties of the cells, how these cell types are connected with each other, and how they work together to process and make sense of the visual information the brain receives from the outside world. This will ultimately shed light on the inner workings of the brain."

More information: Adult mouse cortical cell taxonomy revealed by single cell transcriptomics, *Nature Neuroscience*, DOI: 10.1038/nn.4216