A cellular community in the brain drives Alzheimer's disease, large-scale analysis reveals

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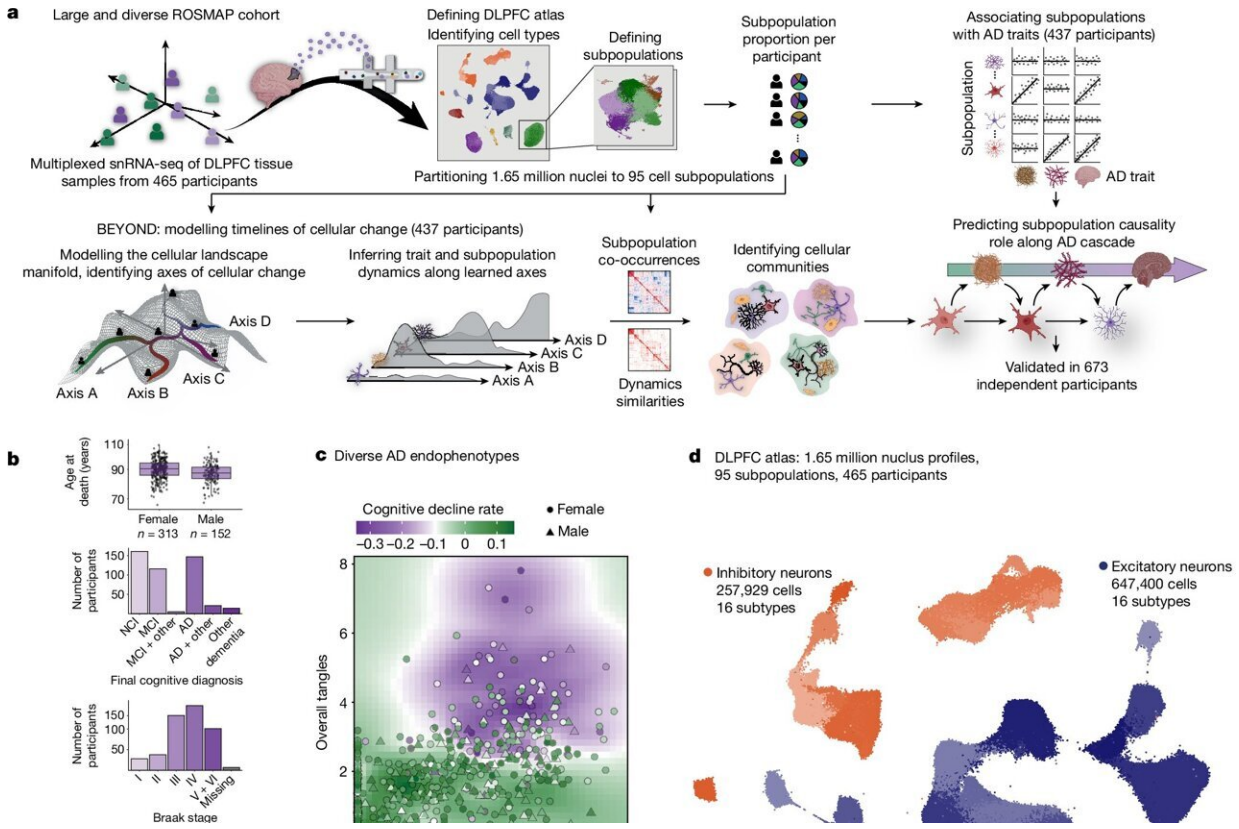

Cellular atlas of the human aged DLPFC in older individuals. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07871-6

An analysis of more than 1.6 million brain cells from older adults has

captured the cellular changes that occur in the early stages of Alzheimer's disease, potentially revealing new routes for preventing the most common cause of dementia in older individuals.

The study also identified a second community of cells that drives the older brain down a different path that does not lead to Alzheimer's disease.

"Our study highlights that Alzheimer's is a disease of many cells and their interactions, not just a single type of dysfunctional cell," says Columbia neurologist Philip De Jager, who led the study with Vilas Menon, assistant professor of neurological sciences at Columbia University Vagelos College of Physicians and Surgeons, and Naomi Habib of the Hebrew University of Jerusalem.

"We may need to modify cellular communities to preserve cognitive function, and our study reveals points along the sequence of events leading to Alzheimer's where we may be able to intervene."

The research is published in the journal *Nature*.

Crunching data from 1.6 million brain cells

The study was a technical marvel, cleverly combining new molecular technologies, machine-learning techniques, and a large collection of brains donated by aging adults.

Though previous studies of brain samples from Alzheimer's patients have provided insights into molecules involved in the disease, they have not revealed many details about where in the long sequence of events leading to Alzheimer's those genes play a role and which cells are involved at each step of the process.

"Past studies have analyzed brain samples as a whole and they lose all cellular detail," De Jager says. "We now have tools to look at the brain in finer resolution, at the level of individual cells. When we couple this with detailed information on the cognitive state of brain donors before death, we can reconstruct trajectories of brain aging from the earliest stages of the disease."

The new analysis required over 400 brains, which were provided by the Religious Orders Study and the Memory & Aging Project based at Rush University in Chicago.

Within each brain, the researchers collected several thousand cells from a brain region impacted by Alzheimer's and aging. Every cell was then run through a process—single-cell RNA sequencing—that gave a readout of the cell's activity and which of its genes were active.

Data from all 1.6 million cells were then analyzed by algorithms and machine-learning techniques developed by Menon and Habib to identify the types of cells present in the sample and their interactions with other cells.

"These methods allowed us to gain new insights into potential sequences of molecular events that result in altered brain function and cognitive impairment," Menon says. "This was only possible thanks to the large number of brain donors and cells the team was fortunate enough to generate data from."

Aging vs. Alzheimer's

Because the brains came from people at different points in the disease process, the researchers were able to solve a major challenge in Alzheimer's research: identifying the sequence of changes in cells involved in Alzheimer's and distinguishing these changes from those

associated with normal brain aging.

"We propose that two different types of microglial cells—the immune cells of the brain—begin the process of amyloid and tau accumulation that define Alzheimer's disease," De Jager says.

Then after the pathology has accumulated, different cells called astrocytes play a key role in altering electrical connectivity in the brain that leads to cognitive impairment. The cells communicate with each other and bring in additional cell types that lead to a profound disruption in the way the human brain functions.

"These are exciting new insights that can guide innovative therapeutic development for Alzheimer's and brain aging," De Jager says.

"By understanding how individual cells contribute to the different stages of the disease, we will know the best approach with which to reduce the activity of the pathogenic cellular communities in each individual, returning brain cells to their healthy state," De Jager says.

More information: Naomi Habib, Cellular communities reveal trajectories of brain ageing and Alzheimer's disease, *Nature* (2024). DOI: 10.1038/s41586-024-07871-6.
www.nature.com/articles/s41586-024-07871-6

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