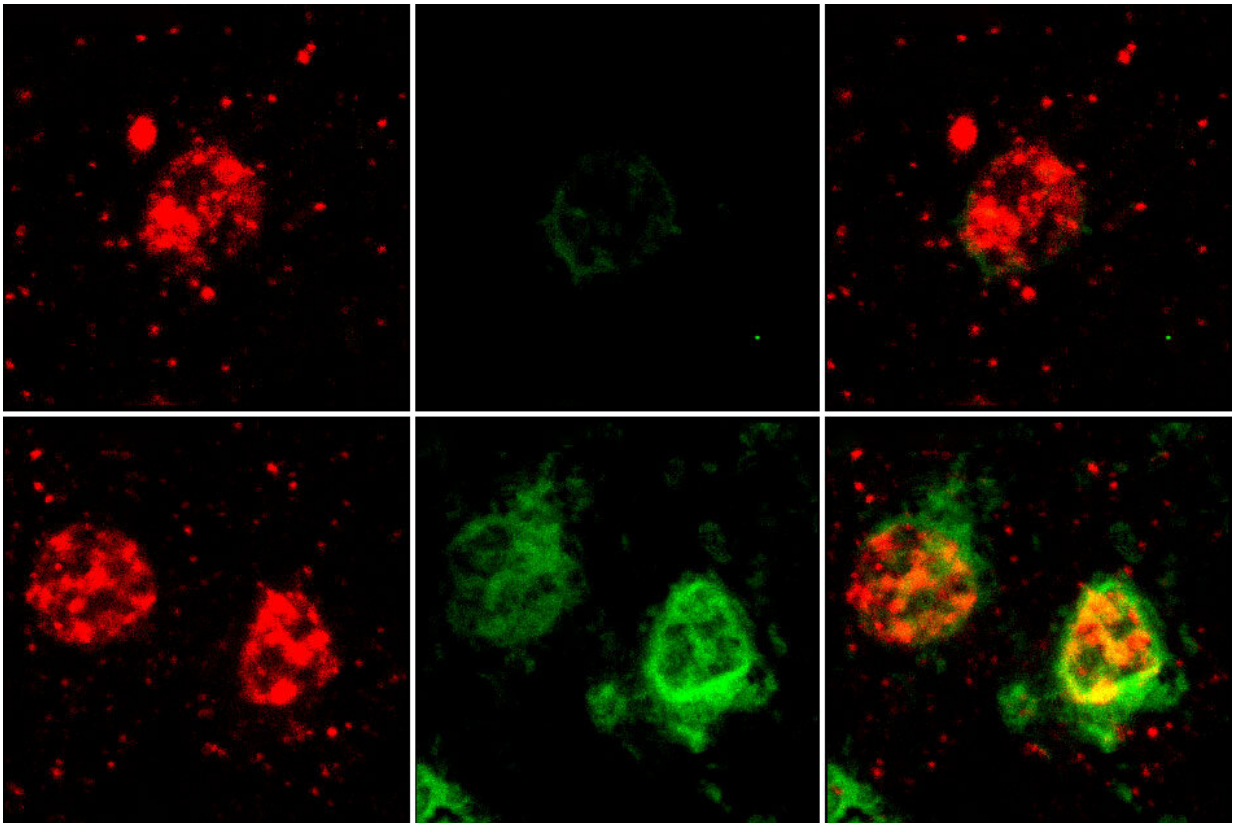


A comprehensive map of how Alzheimer's affects the brain

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Oligodendrocytes from a patient with Alzheimer's (bottom row) and a non-Alzheimer's subject (top row) are labeled in red. The green stain reveals a protein encoded by a gene called QDRP, which MIT researchers found is expressed at much higher levels in oligodendrocytes from Alzheimer's patients. Credit: Zhuyu Peng

MIT researchers have performed the first comprehensive analysis of the genes that are expressed in individual brain cells of patients with Alzheimer's disease. The results allowed the team to identify distinctive cellular pathways that are affected in neurons and other types of brain cells.

This analysis could offer many potential new drug targets for Alzheimer's, which afflicts more than 5 million people in the United States.

"This study provides, in my view, the very first map for going after all of the molecular processes that are altered in Alzheimer's disease in every single cell type that we can now reliably characterize," says Manolis Kellis, a professor of computer science and a member of MIT's Computer Science and Artificial Intelligence Laboratory and of the Broad Institute of MIT and Harvard. "It opens up a completely new era for understanding Alzheimer's."

The study revealed that a process called axon myelination is significantly disrupted in patients with Alzheimer's. The researchers also found that the brain [cells](#) of men and women vary significantly in how their [genes](#) respond to the disease.

Kellis and Li-Huei Tsai, director of MIT's Picower Institute for Learning and Memory, are the senior authors of the study, which appears in the May 1 online edition of *Nature*. MIT postdocs Hansruedi Mathys and Jose Davila-Velderrain are the lead authors of the paper.

Single-cell analysis

The researchers analyzed postmortem brain samples from 24 people who exhibited high levels of Alzheimer's disease pathology and 24 people of similar age who did not have these signs of disease. All of the subjects

were part of the Religious Orders Study, a longitudinal study of aging and Alzheimer's disease. The researchers also had data on the subjects' performance on cognitive tests.

The MIT team performed single-cell RNA sequencing on about 80,000 cells from these subjects. Previous studies of gene expression in Alzheimer's patients have measured overall RNA levels from a section of brain tissue, but these studies don't distinguish between cell types, which can mask changes that occur in less abundant cell types, Tsai says.

"We wanted to know if we could distinguish whether each cell type has differential gene expression patterns between healthy and diseased brain tissue," she says. "This is the power of single-cell-level analysis: You have the resolution to really see the differences among all the different cell types in the brain."

Using the single-cell sequencing approach, the researchers were able to analyze not only the most abundant cell types, which include excitatory and inhibitory neurons, but also rarer, non-neuronal brain cells such as oligodendrocytes, astrocytes, and microglia. The researchers found that each of these cell types showed distinct gene expression differences in Alzheimer's patients.

Some of the most significant changes occurred in genes related to axon regeneration and myelination. Myelin is a fatty sheath that insulates axons, helping them to transmit electrical signals. The researchers found that in the individuals with Alzheimer's, genes related to myelination were affected in both neurons and oligodendrocytes, the cells that produce myelin.

Most of these cell-type-specific changes in gene expression occurred early in the development of the disease. In later stages, the researchers

found that most [cell types](#) had very similar patterns of gene expression change. Specifically, most brain cells turned up genes related to stress response, programmed cell death, and the cellular machinery required to maintain protein integrity.

Sex differences

The researchers also discovered correlations between gene expression patterns and other measures of Alzheimer's severity such as the level of amyloid plaques and neurofibrillary tangles, as well as cognitive impairments. This allowed them to identify "modules" of genes that appear to be linked to different aspects of the disease.

"To identify these modules, we devised a novel strategy that involves the use of an artificial neural network and which allowed us to learn the sets of genes that are linked to the different aspects of Alzheimer's disease in a completely unbiased, data-driven fashion," Mathys says. "We anticipate that this strategy will be valuable to also identify gene modules associated with other brain disorders."

The most surprising finding, the researchers say, was the discovery of a dramatic difference between brain cells from male and female Alzheimer's patients. They found that excitatory neurons and other brain cells from male patients showed less pronounced gene expression changes in Alzheimer's than cells from female individuals, even though those patients did show similar symptoms, including amyloid plaques and cognitive impairments. By contrast, brain cells from female patients showed dramatically more severe gene-expression changes in Alzheimer's disease, and an expanded set of altered pathways.

"That's when we realized there's something very interesting going on. We were just shocked," Tsai says.

So far, it is unclear why this discrepancy exists. The sex difference was particularly stark in oligodendrocytes, which produce myelin, so the researchers performed an analysis of patients' white matter, which is mainly made up of myelinated axons. Using a set of MRI scans from 500 additional subjects from the Religious Orders Study group, the researchers found that female subjects with severe memory deficits had much more white matter damage than matched male subjects.

More study is needed to determine why men and women respond so differently to Alzheimer's [disease](#), the researchers say, and the findings could have implications for developing and choosing treatments.

"There is mounting clinical and preclinical evidence of a sexual dimorphism in Alzheimer's predisposition, but no underlying mechanisms are known. Our work points to differential cellular processes involving non-neuronal myelinating cells as potentially having a role. It will be key to figure out whether these discrepancies protect or damage the brain cells only in one of the sexes—and how to balance the response in the desired direction on the other," Davila-Velderrain says.

The researchers are now using mouse and human induced pluripotent stem cell models to further study some of the key cellular pathways that they identified as associated with Alzheimer's in this study, including those involved in myelination. They also plan to perform similar gene expression analyses for other forms of dementia that are related to Alzheimer's, as well as other [brain](#) disorders such as schizophrenia, bipolar disorder, psychosis, and diverse dementias.

Provided by Massachusetts Institute of Technology

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