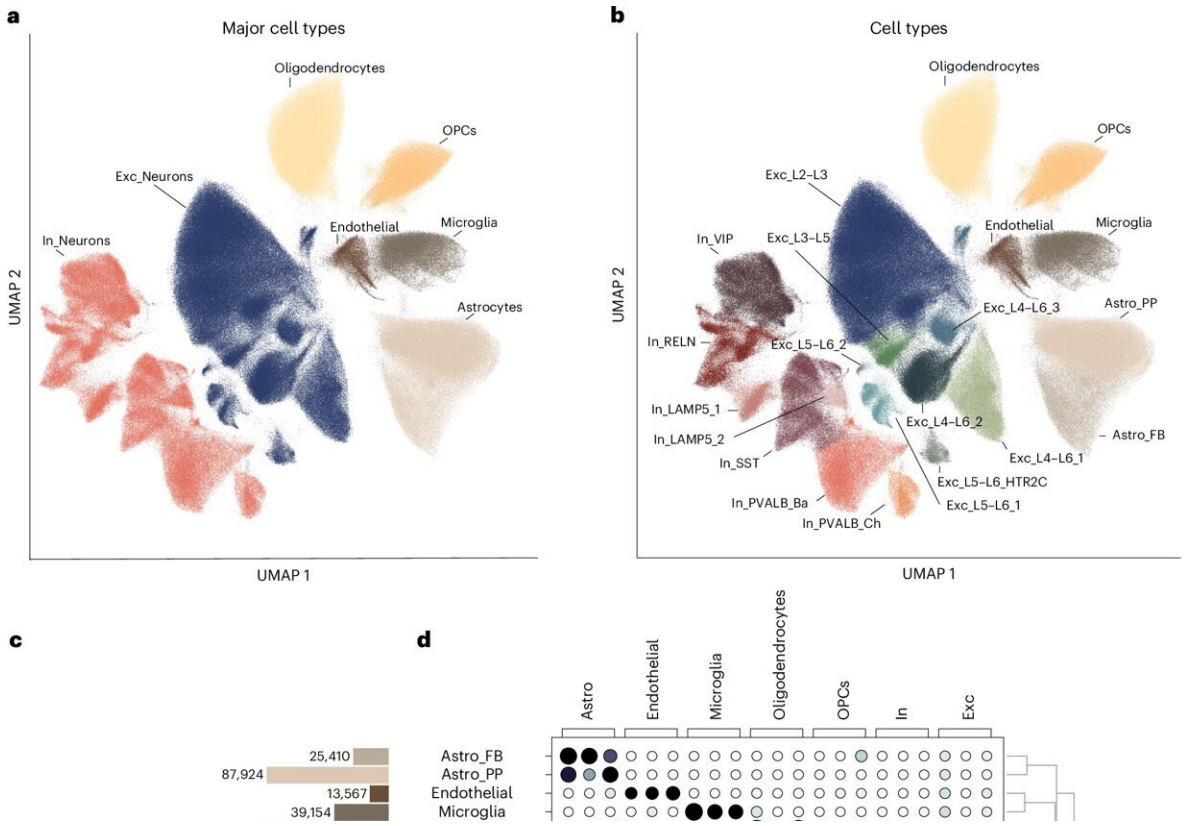
Decoding the aging brain: Changes in gene activity detected in different cell types

September 3 2024, by Anke Schlee



Identification of cell types. **a**,**b**, Uniform manifold approximation and projection (UMAP) showing ~800,000 nuclei from the OFC from 87 donors colored by major cell-type cluster (**a**) and individual cell-type cluster (**b**). Cell-type annotation was performed using a label transfer algorithm, followed by manual curation based on marker genes described in the literature. **c**, Bar plot depicting the number of nuclei per individual cell-type cluster. **d**, Left, dot plot showing the expression of representative marker genes, which are grouped by major cell types. The size of the dot represents the percentage of nuclei expressing the

gene, and the color indicates the mean expression level. Right, dendrogram showing the relationship between identified cell-type clusters based on similarity in gene expression; Astro_FB, fibrous astrocytes; Astro_PP, protoplasmic astrocytes; Exc, excitatory; In, inhibitory; L, cortical layer; Ba, basket; Ch, chandelier; PVALB, parvalbumin. Credit: *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01742-z

Aging is a complex biological process that also takes place in the brain. Researchers have discovered that the gene activity changes in different cell types in the brain. A certain type of neuron is particularly affected. In the long term, the findings could provide starting points for slowing down the aging process and delaying neurodegenerative diseases such as Alzheimer's-type dementia.

The work is published in the journal *Nature Neuroscience*.

As we age, our brain ages too. Every single cell is subject to this process, which is accompanied by changes in gene activity, among other things. Our brain consists of various cell types, each with specific properties, functions and connections, which together perform the brain's complex computations.

Researchers from the Max Planck Institute of Psychiatry wanted to know how the gene activity changes in the different cell types of the brain as we age. To this end, they examined tissue samples from 90 brains of people between the ages of 25 and 85, who had donated their brains to science after their death. The researchers focused on cells from the prefrontal cortex, a region of the brain that is crucial for cognitive processes such as thinking, planning and problem-solving.

Single nucleus RNA sequencing enabled the scientists to investigate

changes in the gene activity of individual cell types over the course of aging for the first time.

"We were able to show that gene expression changes in all cell types during the course of aging, but not necessarily in the same genes," summarizes project leader Anna Fröhlich. She found that in all cell types, the activity of genes that are important for synaptic transmission, i.e., communication between neurons, changes with aging. The activity of genes involved in mRNA processing, i.e. the production of protein molecules, also changes during the aging process.

Comparison with Alzheimer's disease

As age is the greatest risk factor for neurodegenerative diseases such as Alzheimer's disease, the researchers compared the age-related changes in gene expression with changes observed in Alzheimer's disease. They found extensive overlaps in certain cell types. This could indicate that continuous, non-pathological changes exceed a threshold at some point and thus turn pathological, so to speak. It is particularly interesting that a certain cell type of inhibitory neuron appears to be particularly affected by both aging and Alzheimer's disease.

The tissue samples examined came from people with and without psychiatric disorders. A comparison of these two groups showed differences in biological aging: the gene expression age of people with psychiatric illness was accelerated, meaning that they were "biologically" older. This could be because the activity of some genes changes not only with age, but also due to psychiatric disorders, as the scientists were able to show. This could represent a possible explanation as to why people with psychiatric disorders such as schizophrenia might be particularly susceptible to pathological brain aging processes.

The findings could help identify new therapeutic approaches at the

molecular level that could influence the aging process and thus potentially delay dementia. However, this requires extensive further research.

More information: Anna S. Fröhlich et al, Single-nucleus transcriptomic profiling of human orbitofrontal cortex reveals convergent effects of aging and psychiatric disease, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01742-z

Provided by Max Planck Society