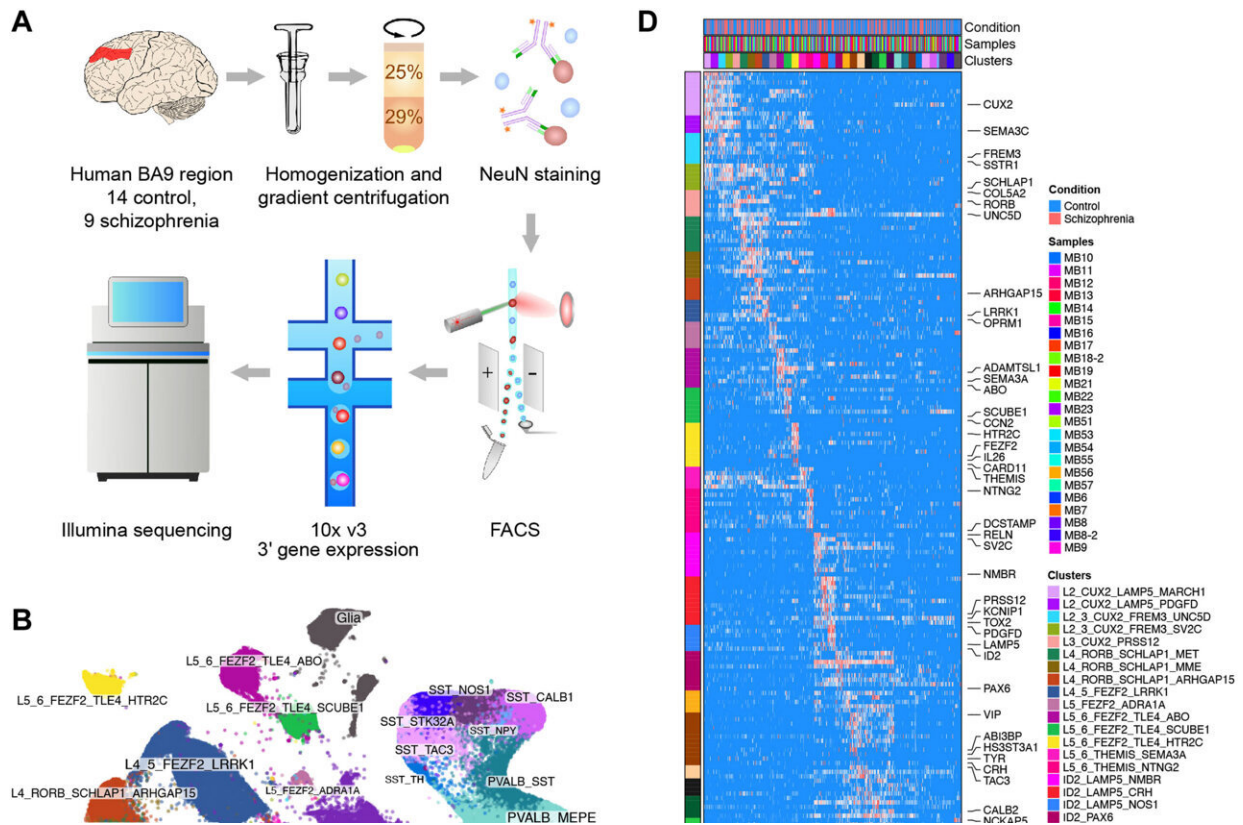


Huge unveiling of schizophrenia brain cells show new treatment targets

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snRNA-seq analysis of the DLPFC from patients with schizophrenia and matched controls. (A) Experimental design of the snRNA-seq measurements. FACS, fluorescence-activated cell sorting. (B) UMAP representation of the measured nuclei, colored by subtypes. (C) Expression of marker genes for major cortical cell types, visualized on the UMAP embedding: GABAergic interneurons, principal neurons, and glia; additional markers distinguish families of GABAergic interneurons and principal neurons. (D) Heatmap showing expression of markers for specific neuronal subtypes. (E) Estimated cortical

layer positions of the neuronal subtypes. These are predictions based on Allen Institute data with manual cortical layer microdissections before nuclei isolation and sequencing. Because of manual layer dissections, small degree of mispositioning of subtypes (e.g., principal neurons in layer 1) is expected. Credit: *Science Advances* (2022). DOI: 10.1126/sciadv.abn8367

If you thought it was easy to analyze brain cells, think again.

When you take a brain tissue sample, all that your analysis would normally show you is an average for all the [cell types](#) present. And since there are a whole lot of cell types in our brain—[neurons](#) and others—you'll get a sort of cell smoothie, which makes it difficult if not impossible to tell the cells apart, let alone study them.

It is like wanting to know how many green M&M's there are in a bowl, but instead just getting told how many colors there are. You are not really getting the answer you wanted.

Now, researchers from the University of Copenhagen applied a new method to analyze neurons one by one in order to reveal hitherto unobtainable information about them.

The researchers specifically studied post mortem brain tissue from [adult patients](#) with [schizophrenia](#) using control samples from non-schizophrenic brains.

"The human brain has very heterogenous tissue with hundreds of neuron types. We identified exactly those neurons that are most affected by schizophrenia, the position of these neurons in the [human brain](#) and what is wrong with these neurons. We see the genes that changed their expression and damaged the overall neuronal signaling, and even how

potential neuronal networks are impaired," explains Konstantin Khodosevich, Group Leader and Associate Professor at the Biotech Research & Innovation Center (BRIC).

What is schizophrenia?

The illness affects and distorts thoughts, feelings and actions. It is a psychosis—a distorted perception of reality—often characterized by delusions and hallucinations.

Around 20 percent of those diagnosed with schizophrenia get better. The remaining 80 percent can have long periods without symptoms, but also periods where the symptoms become so serious that they require hospitalization. The earlier schizophrenia is treated, the better the chances of the treatment producing good results.

Schizophrenia affects around 1,000 Danes each year. In total, up to 30,000 Danes are living with schizophrenia, and half of them are undergoing treatment in the region's Mental Health Centers.

The researchers note that they do see different types of schizophrenia in their analysis, but that they do not have enough data to analyze all the subgroups of the disease.

Next treatment target

By finding the neurons most affected in schizophrenia as a whole, the research team points out that these neurons could very well also be the next treatment target.

"Now that we know the most affected neurons, we can try to target them to alleviate some of the symptoms that come with the disease. We also

now know the [molecular changes](#) in these neurons. This gives us a potential to not only to alleviate the symptoms but also treat schizophrenia early in the therapeutic window, which is during the brain's maturation until 20-25 years of age," says Khodosevich.

The researchers discovered a network of neurons most affected by schizophrenia. In particular, they show that it is the upper layers of the prefrontal cortex, the region of the cortex which is involved in higher cognitive brain functions such as learning and memory and general cognition.

How the study was conducted

The researchers took tissue samples from 25 brains, where half of them had schizophrenia and half did not. They separated around 220,000 neurons in the brain tissue samples with schizophrenia and analyzed them separately.

They found the hotspot region for schizophrenia in the upper prefrontal cortex, which is a one to three millimeter thin line covering frontal part of the brain. The brains with schizophrenia had many more changes in this area than in the non-schizophrenic brain. The researchers found distinct neuronal networks in the upper prefrontal cortex that might be responsible for overall symptoms of the illness.

They also discovered that it is not just one type of neurons that is affected by the disease, but a network of [neuron types](#).

"Our results suggest that for treatment of schizophrenia we should not target one type of neurons, but rather their overall network. Impacting this network or cell ensemble could help restore the impaired function of these neurons," says Konstantin Khodosevich.

It is known from previous research that, on a biological level, the energy production of the neurons in the prefrontal cortex is malfunctioning in schizophrenia. This enhances the developmental processes of these cells. The area as a whole undergoes continuous structural changes through youth and should stop and remain stable from age 20-25 years old. But with schizophrenia, this region in the [brain](#) has growth or enhanced activity, which help produce symptoms.

The research was published in *Science Advances*.

More information: Mykhailo Y. Batiuk et al, Upper cortical layer–driven network impairment in schizophrenia, *Science Advances* (2022). [DOI: 10.1126/sciadv.abn8367](https://doi.org/10.1126/sciadv.abn8367)

Provided by University of Copenhagen

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