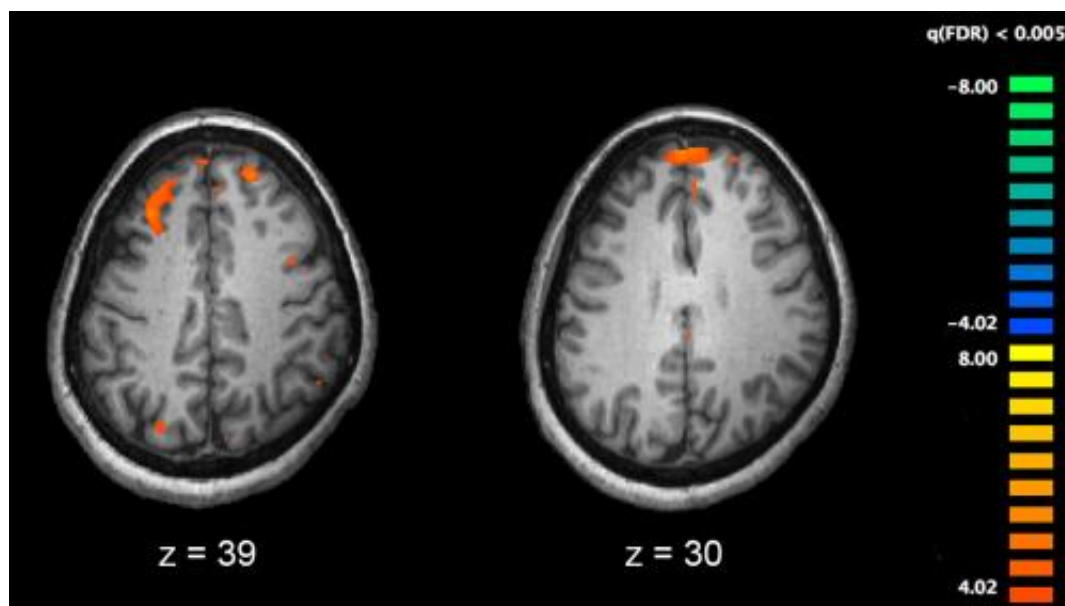


Excess immune pruning of synapses in neural cells derived from patients with schizophrenia

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Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

A study led by Massachusetts General Hospital (MGH) investigators finds evidence that the process of synaptic pruning, a normal part of

brain development during adolescence, is excessive in individuals with schizophrenia. While previous studies have found structural abnormalities in the brains of people with schizophrenia that suggested a role for abnormal synaptic pruning, this study—published in *Nature Neuroscience* - is the first to directly observe excessive synaptic pruning using cells from patients with schizophrenia.

"This approach lets us model at least one of the abnormalities of schizophrenia 'in a dish'," says Roy Perlis, MD, MSc, of the MGH Department of Psychiatry and the Center for Genomic Medicine, senior author of the report. "It is one of the first indications in [cells](#) from patients of what is contributing to the abnormalities in pruning that have been suspected. And we hope to use these cells to screen for new treatments that may ultimately address that abnormality."

Studies in recent years have revealed that microglia, which are innate immune cells active within the [central nervous system](#), play an important role in brain development by removing unneeded synapses—points of communication between [brain cells](#)—and other neural structures. This process is particularly active during adolescence and early adulthood, the time of life when symptoms of schizophrenia and other mental illnesses often first appear.

A new system developed by Perlis's team has made it possible, for the first time, to study synaptic pruning in patient-derived human cells. In an earlier study the investigators described creating induced microglia-like (iMG) cells from monocytes derived from blood samples cultured under special conditions. They then developed a way to measure synaptic pruning by observing those cells devour synaptic structures called synaptosomes isolated from cultured neurons. In the current study they used iMG cells and synaptosomes obtained from men with schizophrenia and from healthy control participants to determine patient versus control differences in the model of synaptic pruning. In addition, they validated

their findings in by growing microglia together with neurons, directly measuring the uptake by microglia of synaptic markers from the neurons.

Their experiments showed that the engulfment and elimination of synapses by iMG cells was most rapid and extensive when both microglia and synapses were derived from men with schizophrenia. Microglia from patients with schizophrenia more extensively pruned synapses from either patients or controls, while control microglial cells ingested the fewest synapses of all. The results suggest that factors from both microglia and neurons contribute to increased synaptic pruning in people with schizophrenia.

Several gene variants have been associated with an increased risk of schizophrenia, and one of those most strongly associated relates to the complement system, which contributes to the ability of immune cells to remove microbes and dying cells. The investigators found that increased expression in neurons of a specific complement protein variant was associated with increased synaptic uptake by iMG cells, although that variant is not the only contributor to increased microglial uptake.

Since preclinical research has suggested that the antibiotic drug minocycline might have benefits against neurodegenerative diseases, although the mechanism is not known, the investigators pretreated microglial cell cultures with a range of minocycline doses before applying the cells to neurons derived from patients with schizophrenia and from controls. The highest minocycline doses almost totally eliminated synaptic engulfment.

To investigate whether minocycline, which is often prescribed to treat acne, might also decrease schizophrenia risk in humans by reducing synaptic pruning during adolescence, the researchers analyzed data from up to 10 years of electronic health records from two academic medical

centers. Of more than 22,000 individuals prescribed at least one of five common antibiotics between the ages of 10 and 18, 203 subsequently were diagnosed with a psychotic disorder. The more than 3,800 individuals who were treated with minocycline or the related antibiotic doxycycline for at least 90 days had a significantly reduced risk of a subsequent psychotic disorder diagnosis than did those receiving other antibiotics.

"As encouraged as we are by these initial results, they represent a first step," says Perlis, a professor of Psychiatry at Harvard Medical School. "Although we studied cells from more patients than any previous study we're aware of, we need even larger numbers to better understand what is different in cells from individuals with [schizophrenia](#). There is reason to be hopeful that we are starting to understand what causes this devastating disorder as a first step towards developing strategies to prevent, not just treat it. But there is also much more work to be done."

More information: Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning, *Nature Neuroscience* (2019). DOI: [10.1038/s41593-018-0334-7](https://doi.org/10.1038/s41593-018-0334-7) , www.nature.com/articles/s41593-018-0334-7

Provided by Massachusetts General Hospital

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