The infection connection
Following large outbreaks of influenza in the 1800s and 1900s, including the 1918 flu pandemic, physicians took note of an uptick in patients exhibiting mental disturbances, particularly delusions and hallucinations. Such cases were so common that medical professionals at the time even coined the term “psychoses of influenza” to describe this condition. “There were records of influenza pandemics whereby people acutely affected with influenza acted in ways consistent with what we now understand to be psychosis,” says Thomas Pollak, a neuropsychiatrist and clinical lecturer at King’s College London in the UK.

This type of infection-triggered psychosis was not unique to influenza. Many other instances of psychiatric symptoms developing after encountering a pathogen have been documented throughout history. Neurosyphilis, for example, occurs when the bacterium Treponema pallidum invades the central nervous system, causing psychosis and depression, among other schizophrenia-like symptoms. When the link with the syphilis-causing microbe was established, some mental institutions reported that the symptoms in around a third of their patients could be attributed to the infectious disease. Other examples include Toxoplasma gondii, a parasite that commonly infects cats: anti-Toxoplasma antibodies have been observed in the blood of some patients, suggesting that exposure to the parasite might trigger schizophrenia. And during the COVID-19 pandemic, cases of psychosis following a SARS-CoV-2 infection among people with no history of mental illness have emerged all around the globe.

Some data suggest that maternal exposure to infections may heighten the risk of offspring developing conditions such as schizophrenia. Numerous studies have found that children who are born in the winter or spring—when infectious agents tend to circulate—are at a greater risk for schizophrenia and other mental illnesses than those born during another season. There are also reports of maternal influenza infections increasing the risk of psychosis, although this link has not been consistently found.

More-recent evidence has also emerged from large epidemiological studies in Scandinavia, where researchers have access to nationwide registries containing medical data and other personal information. A series of studies using such data in Denmark from a group led by Michael Benros, a professor of immunopsychiatry at the University of Copenhagen, revealed that as an individual’s number of infections increased, the subsequent risk of developing a schizophrenia spectrum disorder—a cluster of mental illnesses that share similar features, including psychosis—increased in a dose-

AUTOIMMUNE UNDERPINNINGS OF PSYCHOSIS
One of the most well-known autoantibodies with targets in the brain is the anti-NMDAR antibody, which targets the NMDA receptor (NMDAR) that is found on excitatory neurons in the brain. When present, this autoantibody prompts neurons to engulf NMDARs and reduces these receptors’ numbers at the synapse. This dearth of NMDARs, in turn, causes problems in synaptic transmission that underlie a range of neuropsychiatric symptoms such as hallucinations, delusions, seizures, and movement abnormalities. Researchers have pinpointed more than two dozen other brain-targeting antibodies, most of which are found in patients with autoimmune disease of the central nervous system. The role these antibodies play in psychiatric illnesses such as schizophrenia is the subject of active investigation.