

Scientists begin to unravel the mysteries of the coronavirus and brains

By Ben Guarino and Frances Stead Sellers

June 7, 2021 at 10:30 a.m. CDT

   412

In the coronavirus pandemic's early weeks, in neuropathology departments around the world, scientists wrestled with a question: Should they cut open the skulls of patients who died of covid-19 and extract their brains?

Autopsy staff at Columbia University in New York were hesitant. Sawing into bone creates dust, and the Centers for Disease Control and Prevention had issued a warning about the bodies of covid patients — airborne debris from autopsies could be an infectious hazard.

But as more patients were admitted and more began to die, researchers decided to “make all the efforts we could to start collecting the brain tissue,” Columbia neuropathologist [Peter D. Canoll](#) said.

In March 2020, in an isolation room, the Columbia team extracted a brain from a patient who had died of severe covid-19, the illness caused by the coronavirus. During the next months, they would examine dozens more. Saw met skull elsewhere, too. In Germany, scientists autopsied brains — even though medical authorities recommended against doing that.

Researchers were searching the brain for damage — and for the virus itself. At the pandemic's start, understanding how the virus affected the nervous system was largely a mystery. S. Andrew Josephson, chair of neurology at the University of California at San Francisco and editor in chief of the academic journal *JAMA Neurology*, said, “We had hundreds of submissions of ‘I saw one case of X.’” It was difficult to understand whether single cases had any relationship to covid-19 at all.

Patients reported visual and auditory disturbances, vertigo and tingling sensations, among other perplexing symptoms. Some lost their sense of smell, or their vision became distorted. Weeks or months after the initial onset of symptoms, some remain convinced after even a mild bout of the coronavirus of persistent “brain fog.”

Even as the pandemic appears [ready to recede](#) in the United States, dropping below an average of 20,000 new cases daily, it will take years to more fully understand the way the virus afflicts the brain. Autopsies of the sickest covid patients have revealed clotting in the brain and other signs of acute damage. They offered little evidence the virus attacks the organ directly. Beyond that, many other neurological details of covid remain unknown.

Many neurologists, including Josephson, suspect the virus is often to blame, even if the mechanism is not yet understood.

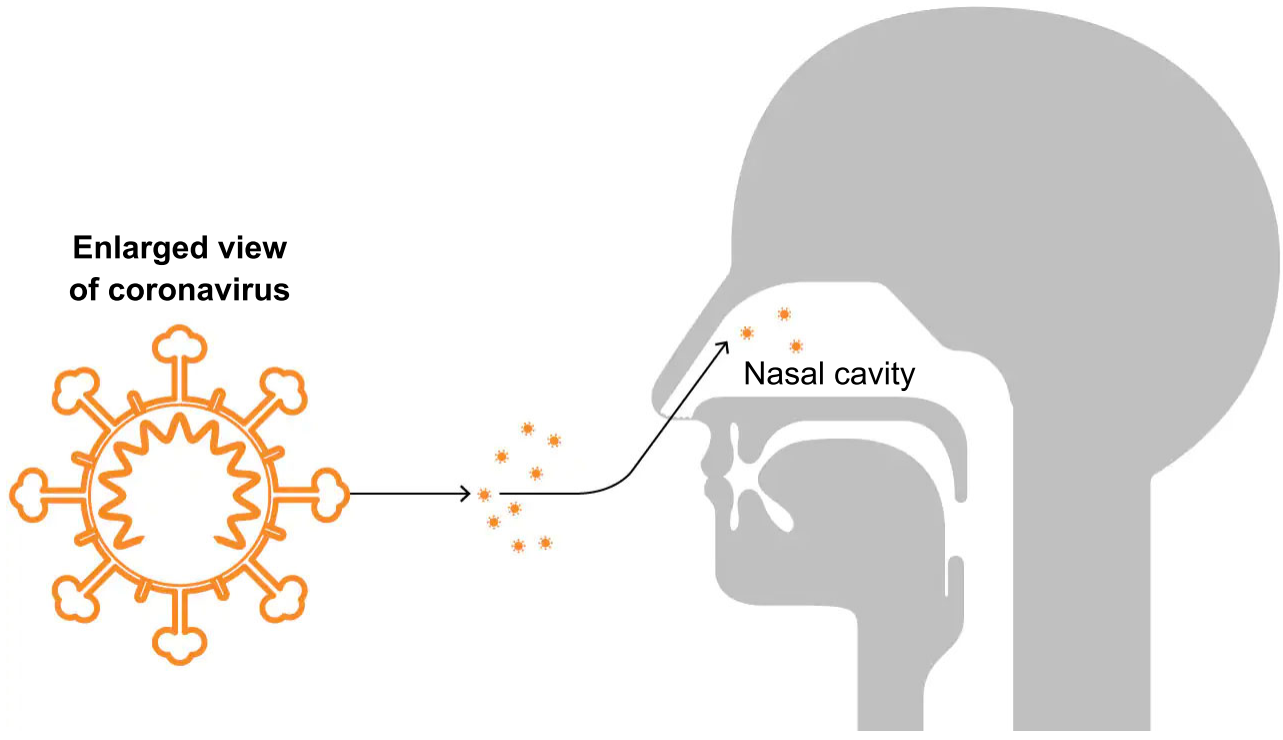
“We are now convinced that there is something neurologically, both acutely and non-acutely,” he said.

Josephson has a hunch the coronavirus could be acting like herpes simplex, which commonly causes cold sores and in rare cases, dangerous brain swelling known as [encephalitis](#). That swelling triggers the immune system. And sometimes, weeks or months later, the patient deteriorates not because of the virus but because of an autoimmune attack.

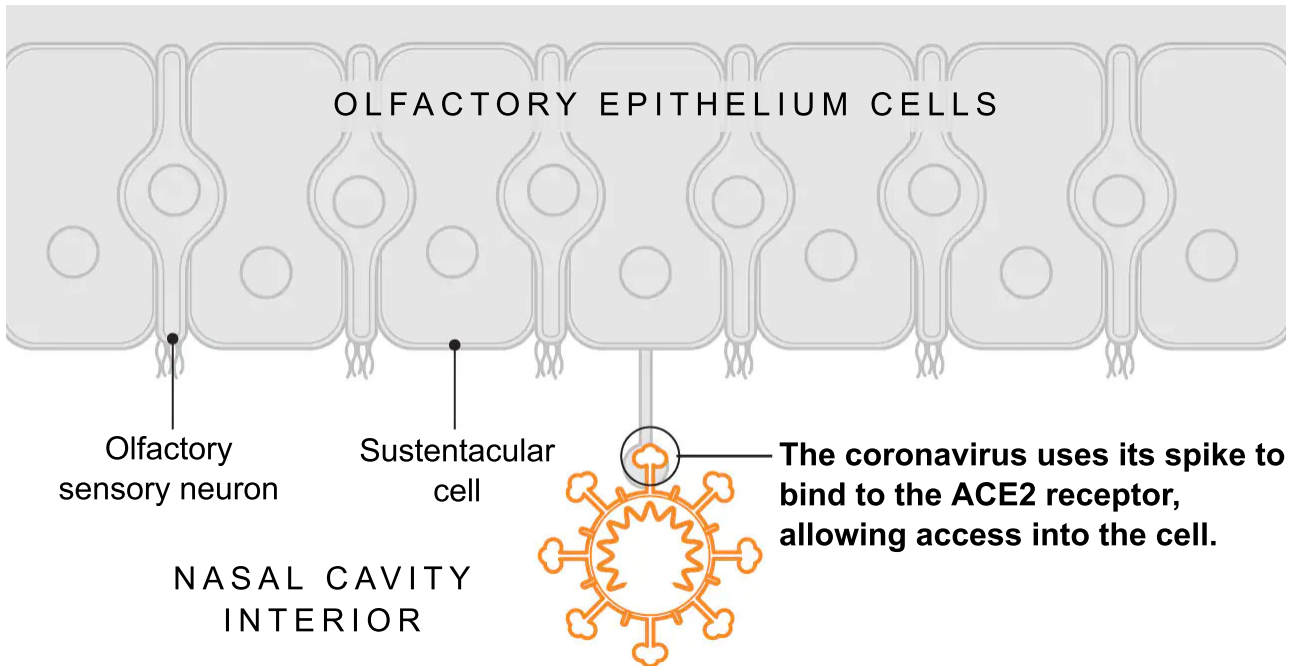
“It's a wonderful analogy,” Josephson said. “An initial viral infection, an antibody response and persistent neuropsychiatric problems.”

Hunting for the coronavirus in the brain

Most coronavirus infections begin with pathogens breathed in while suspended inside tiny droplets of body fluid someone else expelled. These infectious parcels can be smaller than the nostrils they pass through by a factor of thousands — picture, for a similar sense of scale, being sucked into a mile-high maw of a tunnel.

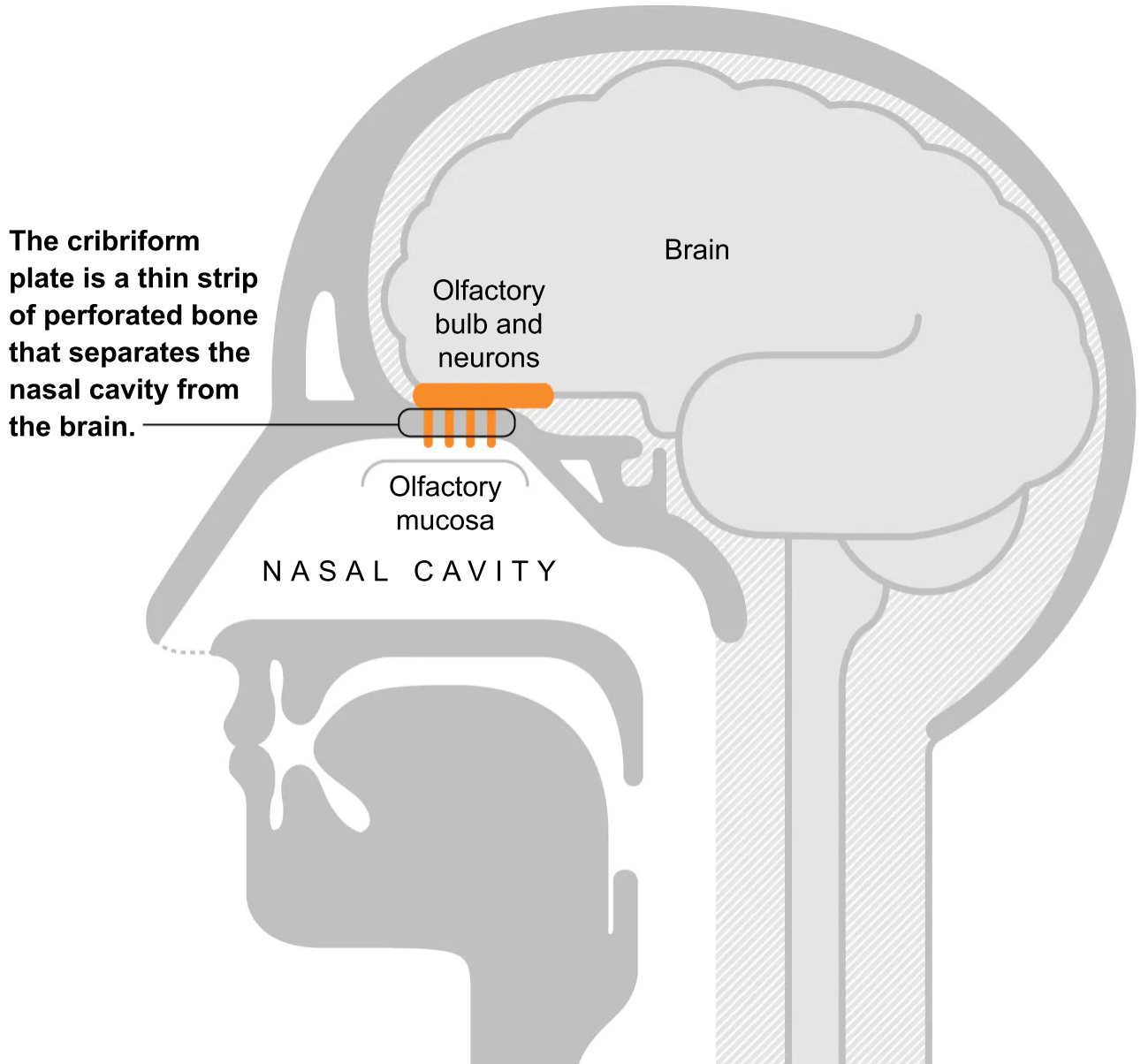


Once inside, the virus begins to hijack cells lining the respiratory system. It exploits a human protein called an ACE2 receptor.



This receptor studs the surface of many cells in our respiratory passages. The virus uses its spike protein like a skeleton key to ease open cells. Cells in the nasal cavity appear particularly susceptible to an infestation of the coronavirus. Virus in the upper part of the nasal cavity, the olfactory mucosa, probably causes the loss of smell experienced by some people with covid.

The olfactory mucosa sits below a thin strip of perforated bone, known as the cribriform plate. Sensory neurons are threaded from above through those holes. The brain rests on the other side of that thin bone.



AARON STECKELBERG/THE WASHINGTON POST

It's clear the virus can get very close to the brain. What's less certain is whether virus is able to penetrate deeper and invade it. This isn't simply an academic question — it has medical consequences.

“A person who has virus in their brain can have symptoms related to brain involvement,” such as meningitis or encephalitis, said [Kiran T. Thakur](#), a neurologist at Columbia University Irving Medical Center in New York.

Viruses that invade the brain are tough to eradicate because a barrier protects the brain from the rest of the body. Once viruses enter the brain, Thakur said, the organ can become a refuge for stowaways.

In laboratory experiments, the coronavirus can infiltrate neurons and other brain cells when those cells are cultured. It also can invade clumps of cells designed to replicate the structure of a brain, which scientists call organoids. Those observations suggest brains are vulnerable to invasion by SARS-CoV-2.

At least in theory. Not all brain specialists are convinced that what can happen in a petri dish occurs in sick humans.

“Frankly, I don’t think it tells us a lot about what’s going on in the brains of people who were infected with this virus,” said [James E. Goldman](#), a neuropathologist and a colleague of Thakur and Canoll at Columbia.

As that trio and their co-authors reported in the [journal Brain in April](#), they did not find viral proteins in brain autopsies.

They detected no or low levels of viral RNA, depending on the technique used. Canoll suggested the viral genetic material they did find in the brain came from virus in the membrane that surrounds the brain, not from within the organ itself.

“This, alongside other studies, is suggestive that there’s not a florid amount of virus in the brain in patients who have died,” said Thakur, lead author of that report.

At Berlin’s Charité hospital, neuropathologist Frank Heppner and his colleagues likewise reported high levels of virus in the nasal cavity but limited signs of virus deeper in the brain in a paper published last fall in [Nature Neuroscience](#). The highest virus load was in the olfactory mucosa, and the amount of virus “decreases the more you go up to the brain,” he said.

Heppner and his fellow scientists have studied the brains of more than 100 covid patients. He said the not-yet-published findings from those investigations show low amounts of virus in the brain, too.

A matter of damage

Although there wasn’t much virus to be found, the brains of people killed by the coronavirus weren’t unscathed. The Columbia researchers, looking at thin slices of brain tissue under microscopes, found two main types of problems in patients who died of covid.

First were infarctions, dead tissue surrounding blocked blood vessels, found in the brain’s gray matter. “If you get a blood clot in a blood vessel, it completely obstructs blood flow and therefore oxygenation past that blood clot,” Goldman said. Without oxygen, the tissue dies.

Some of these areas were visible only under a microscope. The sites where the clots had been looked like bruised circles, ringed by junk from partially destroyed cells. Red blood cells spilled out of the damaged vessels.

The second issue, appearing in the brainstem, cerebellum and other areas, involved swarms of immune cells. Those cells often converged around dead or dying neurons. “They’re actually attacking and eating the neurons,” Canoll said.

These immune cells, called microglia, were enlarged and had clustered in nodules, signaling inflammation, though not as severe as what pathologists see in cases of viral encephalitis. Curiously, there was no virus in the neurons being surrounded.

Still, microglia don’t act like this unless provoked.

“Something is triggering them to do that,” said immunologist Lena Al-Harhi, who studies at Rush University in Chicago how HIV affects the central nervous system. That trigger remains unknown, but Harhi suggested it could be an autoimmune response.

While HIV suppresses immunity, covid results in “an immune system on steroids,” she said. This hyper-reaction can include the release of autoantibodies, molecules released by the immune system that end up harming a person’s own cells or tissues. Autoantibodies have been found in postmortem brains and the cerebrospinal fluid of covid patients, Harhi said.

It’s unclear whether the pathologies seen in these autopsies could also occur in patients with mild cases, or long-term symptoms. Goldman declined to speculate. These patients, many of whom were admitted to intensive care, had died of severe covid-19.

“This is a series of a small subset of patients, so there’s a selection issue,” Thakur said. But with that caveat and others — variants are spreading that weren’t in the initial wave of the pandemic, for example — she said the results are suggestive that the virus “isn’t entering and propagating and infecting the brain.”

The scientists are working on a follow-up study examining the brains of patients who had covid and recovered but later died. Those observations should help settle whether brains in very sick patients resemble brains in other cases.

Allison Navis, an assistant professor in the division of neuro-infectious diseases at Icahn School of Medicine at New York’s Mount Sinai Hospital, said understanding covid’s neurological effects will also require a better understanding of who may be affected. Patients treated at the hospital’s post-covid center are predominantly White people with private insurance experiencing symptoms, such as fatigue, that may not be as evident in populations facing greater co-morbidities, including communities of color.

“We don’t pick up on these things in people who have chronic medical issues,” Navis said.

Future investigations and other viruses

Compared with almost all other diseases, covid-19 has been studied with unprecedented focus. “No influenza patient has been followed up so intensely,” Heppner said. This “opens the possibilities to learn from a brain.”

The autopsies, for instance, examined parts of the nasal cavity and brain infrequently explored. The scientists used tools not typically applied across the brain.

“We’ve already started to look at the brains of patients that don’t have covid” but died of other severe lung diseases, Canoll said. They are seeing pathological changes reminiscent of what they detected in brains from people who died of covid.

There are dangers, too, in specialists attributing occurrences of rare and unexplained neurological disorders to a new disease.

“When covid first started showing up, we were all paying attention,” said Amanda Dean Henderson, a neurophthalmologist at Johns Hopkins Hospital.

A clearer understanding of covid’s impact will involve developing large-scale population studies.

That process is underway — but it may take years.

Danielle R. Reed, associate director of the Monell Chemical Senses Center, a research institute in Philadelphia that advertises its expertise with a big golden nose out front, began hearing early in the pandemic that many covid patients were complaining of an abrupt loss of smell, but didn’t have stuffy noses. Reed helped form the Global Consortium for Chemosensory Research, which now has more than 500 members in dozens of countries investigating anosmia, or loss of the sense of smell.

Andrea B. Troxel, a professor of population health, and her colleagues at the NYU Grossman School of Medicine have been awarded four years of federal funding for their NeuroCOVID Project to create a databank from studies along with a biobank of tissue samples in hopes of shedding light on these neurological mysteries.

Troxel, who continues to be surprised by the new problems associated with covid, said the response has been enormous, both from providers and patients, who believe sharing their experiences may alleviate somebody else's suffering. Ultimately, Troxel hopes the database may allow the development of therapies.

Joanna Hellmuth, a cognitive neurologist at the UCSF Memory and Aging Center, said she hears the same story repeatedly from previously healthy young adults who tell her that after even a mild case of covid: "My brain doesn't work like it used to."

Hellmuth said cognitive impairment is showing up in people who measure well in mood testing, suggesting their symptoms are not caused by depression or another psychiatric problem. She has seen similar patterns caused by other viruses.

"In SARS and MERS, there were neurological issues," she said, referring to outbreaks in 2003 and 2013 involving diseases caused by other coronaviruses. "We didn't come into this pandemic with a good understanding of the neurological issues of coronaviruses."

Unless more research is done this time around, she fears clinicians will be ill-prepared when the next pandemic hits.