Implications on the Forgetfulness due to COVID-19.

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Perspective

Jonathan Aaron, a 40-year-old math teacher in Houston, Tex., relies on his voice to clearly communicate with his high school students. So when he began to feel he was recovering from COVID, he was relieved to get his voice back a month after losing it. Thornton got sick in mid-August and had symptoms typical of a moderate case: a sore throat, headaches, trouble breathing. By the end of September, "I was more or less counting myself as on the mend and healing," Thornton says. "But on September 25, I took a nap, and then my mom called." As the two spoke, Thornton's mother remarked that it was great that his voice was returning. Something was wrong, however.

"I realized that some of the words didn't feel right in my mouth, you know?" he says. They felt jumbled, stuck inside. Thornton had suddenly developed a severe stutter for the first time in his life. "I got my voice back, but it broke my mouth," he says. After relaying the story over several minutes, Thornton sighs heavily with exhaustion. The thought of going back to teaching with his stutter, "that was terrifying," he says.

In November Thornton still struggled with low energy, chest pain and headaches. And "sometimes my heart rate [would] just decide that we're being chased by a tiger out of nowhere," he adds. His stutter only worsened by that time, Thornton says, and he worried that it reflected some more insidious condition in his brain, despite doctors' insistence that the speech disruption was simply a product of stress.

A growing body of evidence warns that the legacy of the pandemic does not necessarily disappear when the novel coronavirus, or SARS-CoV-2, is cleared from the body. Among the millions of people who have survived respiratory complications from COVID-19, many still live with lingering symptoms in the wake of even a mild case of the disease. Neurological symptoms, ranging from fatigue to brain fog to loss of smell, persist after the virus is gone from the body.

An early survey of 153 COVID-19 patients in the U.K. and a more recent preprint study of people hospitalized with the disease in Italy both found that about a third had neurological symptoms of some kind. Other estimates have trended even higher. "There's a really wide spectrum of [neurological] manifestations of COVID," says Thomas Pollak, a neuropsychiatrist at King's College London and a co-author of the U.K. study. "Some are totally devastating, like stroke or encephalitis, and some are much more subtle." Increasingly common symptoms include fatigue and memory problems—and, at times, new cases of psychosis or mania.

Some neurological manifestations of post-COVID, such as stuttering, are more bizarre than others. But Houston's Thornton is not the only one afflicted. Soo-Eun Chang, a neuroscientist at the University of Michigan, is among the few researchers investigating stutter. "While stress and anxiety are not the cause of stutter, they do exacerbate it," Chang says, and that is true for Thornton. But she says the origins of the disorder lie in complex circuits of the brain that coordinate the millions of neuronal connections needed for human speech.

While most people develop this disruption of speech when they learn to talk, around age two, neurogenic stutter can arise after brain trauma, such as an injury. Chang says her colleagues in clinical practice have reported seeing an increase in cases of stuttering during the pandemic—mostly in people whose existing stutter worsened or whose childhood stutter returned.

Having the virus, she says, could lead to conditions that disrupt speech. "Speech is one of the more complex movement behaviors that humans perform," Chang says. "There are literally 100 muscles involved that have to coordinate on a millisecond time scale, so it's a significant feat. And it depends on a well-functioning brain." COVID's inflammatory response could undermine the efficiency of these circuits. "An immune-mediated attack on synaptic connections could lead to a change in brain function," she says.

The idea that SARS-CoV-2 can get into the human brain is mainly supported by autopsy studies, such as one by Frank Heppner, a neuropathologist at Charité–University Medicine Berlin, and his colleagues. The researchers found evidence of the virus in specific areas of the brain, probably near the sites of entry. One could be the lining of the nasal passage, the olfactory mucosa, which is in close contact with neuronal cells that could provide a route to the brain. "We started at that region and then physically mapped [a pathway through] the regions up to the olfactory bulb and further to brain stem nuclei," Heppner says. The researchers found evidence of viral protein in those distant brain stem regions but not in other areas of the brain. "This told us, or made it likely, that the virus used the transmucosal route along the olfactory nerve as a port of entry," Heppner adds.

They also saw viral particles in trigeminal nerves, which are sensory nerves that enter the brain and transmit the pain of headache. Heppner says his team also discovered hints that the virus could get into the brain through blood vessels. But autopsies were undertaken in those with severe disease, and it is uncertain whether the virus gets into the brain in milder cases. For most people, the symptoms brought on by COVID are likely the result of immune system activity. "The virus gets cleared from the lungs, but the immune system is triggered and doing harmful things," Heppner says. "The same could be true for the

central nervous system. It's a fair speculation. It could explain very well the long COVID symptoms like chronic fatigue and problems in concentration."

William Banks, who studies the blood-brain barrier (BBB) at the Department of Veterans Affairs Puget Sound Health Care System in Washington State and the University of Washington Medical School, says, "The virus doesn't have to get into the brain to muck up function. We know there's a big cytokine storm," meaning the release of inflammatory signals by immune cells in serious cases. Even mild cases provoke cytokine release, however and Banks says it is well established that "cytokines can cross the blood-brain barrier and cause depression like symptoms." Researchers refer to those symptoms—including a loss of interest in life, an increased desire to rest and sleep and cognitive impairments—as "sickness behavior," which often accompanies a flu or cold. Those symptoms could drag on if cytokines continue to be released after the infection has passed.

Yet another possibility is that the virus itself does not cross the BBB but that a viral protein, perhaps shed from a dying virus, might do so. Banks and his colleagues showed as much in a recent paper in Nature Neuroscience. They injected mice with S1, which makes up half of SARS-CoV-2's "spike" protein, and found that it readily crossed the BBB. Michelle Erickson, who works with Banks at the VA Puget Sound and the University of Washington Medical School, says that the work "adds, at least in mice, a defined route by which the virus can get into brain, importantly, in the absence of inflammation," when the blood-brain barrier might be leaky. "We saw that spike can get into the intact BBB," she adds. "Often infiltration is almost entirely due to BBB disruption. But here it was only slightly disrupted, which was quite surprising to us."

The results hint that not only the S1 protein but potentially the virus itself could cross the BBB. A viral protein could cause damage by binding to proteins on neurons and other critical brain cells. "We know these binding proteins are very neurotoxic; they're stress inducing," Banks says. And the presence of any viral material could "shoot off the immune system."

There is yet another possibility: the virus could lead the immune system to produce damaging autoantibodies. These proteins bind not only to the virus but to other proteins in the body as well, either disrupting their function directly or triggering an immune attack on cells. "COVID wreaks havoc with the immune system," says neuropsychiatrist Pollak. "There's a huge surge in various inflammatory mediators." Some early evidence suggests that anti-SARS-CoV-2 antibodies may react to tissues in the brain and body, he says, and that could possibly occur at neurons.

Auto-antibodies are the culprit in a recently described neurological disease called anti-NMDA receptor encephalitis, which can cause fatigue, brain fog, and even psychosis and coma. The immune system proteins bind to NMDA receptors that are critical for neuronal signaling. "Binding to neuronal proteins tends to disrupt synaptic function, like in the case of anti-NMDA receptor antibodies," Pollak says. "That leads to signaling dysfunction, and information processing gets out of whack."

The autoantibody hypothesis still warrants further research. "It's probably the most speculative and the one we know the least about," Banks says. Fatigue, brain fog and other symptoms probably arise from multiple different immune-mediated mechanisms. But researchers agree that synapses, where brain signals are passed from neuron to neuron, are probably disrupted. "We're a long way off from understanding exactly how these nebulous responses arise," Pollak says. "But the general principle is that if you create a perturbation in the system or the brain, you'll affect its computational ability."

Recent pre-print work by Andrew Yang at the laboratory of Tony Wyss-Coray of Stanford University also hints that the brain undergoes widespread changes in the wake of COVID-19 that could contribute to neurological symptoms. Yang and his colleagues found altered patterns of genes switching on and off in cells from the brains of patients who had died of the disease. These differences were observed in neurons and other brain cells—glia and immune cells called microglia. The genetic activation patterns differed from those observed in people who died of the flu or non-viral causes.

Yang's team examined an area of the cortex and saw dramatic gene expression changes in neurons in a specific region called cortical layer. These neurons have been recently implicated as playing a pivotal role in the complex processing required for human thought, so disruption of their activity could lead to mental fuzziness.

The patterns of genetic changes the researchers saw in the cortex mirrored genetic pathways mapped out in mental illnesses such as schizophrenia and depression. In addition, Yang also found gene-expression changes in microglia, which clean up waste and eat dead cells in a process called phagocytosis. Microglia can consume, or phagocytose, neuron bodies and synapses, reshaping neural circuits if the cells are dying or even when they are under stress. Neurons generally do not regenerate, so cognitive function may be impaired.

It is not only neurological symptoms that afflict patients. More common mental illnesses are affecting people with COVID, too. A study published in the Lancet Psychiatry showed that having the disease led to greater risk for anxiety, depression and sleep disorders. Paul Harrison of the University of Oxford and his colleagues sifted through the electronic health records of nearly 70 million Americans and identified more than 62,000 people who had been diagnosed with COVID-19. In the three months following diagnosis, "we found that COVID was associated with roughly twice the incidence of common psychiatric diagnoses, compared with other health conditions," Harrison says.

Why COVID increased the risk for mental illness remains unclear. But Harrison says the virus itself is probably not directly responsible. He points to the psychological consequences of having a potentially fatal illness that could prevent you from returning from the hospital to your family. "There are all sorts of acute stresses associated with the diagnosis," he says. "I think

those factors are going to be the most important explanation for the association we observed." Still, Harrison adds that the immune response provoked by the virus may have also had an effect on the brain that could have triggered psychiatric symptoms. He has a study underway to investigate the longer-term mental health effects of COVID-19, including symptoms such as brain fog and fatigue.

The legacy of COVID will undoubtedly persist. Although Thornton was still struggling by December, his stutter and energy level had improved, and he had gone back to teaching. "The kids have been really good about it," he says. "It's been a rocky road, but there's light at the end."

Still, the lasting effects could mean not just bothersome symptoms for a few people but a public mental health crisis, Banks says. "It could ultimately turn out that—as horrible as the death rate is, with perhaps one in 1,000 Americans having died—in the end there, could be this legacy affecting up to one in 10," he adds. "And it's probably rooted in neuroimmunity."

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