

Brain fog: New study examines causes of this long-COVID symptom

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Neuropsychiatric symptoms of long COVID, including brain fog, inability to concentrate, and headache, have puzzled researchers and

clinicians, who are hunting for those symptoms' causes. A new study found that neuroinflammation and blood-brain-barrier dysfunction are not likely drivers of the symptoms, giving researchers more clues in their quest to uncover what actually may be the culprit.

Scientists have proposed many potential causes of the neuropsychiatric symptoms—including damage of the blood vessels in the brain, ongoing brain inflammation, and lingering viral infection. This study is the first time researchers have tested a large cohort of people living with long COVID for spinal fluid markers of brain inflammation and blood-brain-barrier dysfunction.

The researchers published their findings [in JAMA Network Open on November 10](#), and the outcome is significant even with the negative finding.

"Our study suggests that interventions that are aimed at quieting brain inflammation likely won't help people with long COVID," says Shelli Farhadian, MD, Ph.D., assistant professor of medicine ([infectious diseases](#)) at Yale School of Medicine (YSM) and first author of the study.

For many years, Farhadian and Serena Spudich, MD, Gilbert H. Glaser Professor of Neurology and senior author, have been studying [neurological abnormalities](#) caused by human immunodeficiency virus (HIV) infection. An important way to assess this is through [cerebrospinal fluid](#) (CSF), which offers a window into the brains of living people.

"It's the only part of the central nervous system that's easily accessible," says Farhadian. "It can and has already told us a lot about the brain and people living with other infections and [inflammatory diseases](#) like multiple sclerosis, HIV, and Parkinson's disease."

Researchers can look at proteins and cells in the spinal fluid to see if there is any neurological dysfunction, including abnormal immune activity or blood-brain-barrier impairment.

Researchers analyze cerebrospinal fluid and blood for signs of dysfunction

Beginning in late 2020, the team began enrolling participants with self-reported neurological or psychiatric long COVID symptoms. Many of the patients were enrolled in the YSM Department of Neurology's neuroCOVID clinic. The researchers had to rely on the self-reporting of symptoms because there are no established diagnostic criteria for long COVID.

As a control, researchers were able to use CSF and [blood samples](#) that predated COVID-19. "It's increasingly difficult to find people who have never had COVID-19," says Farhadian.

"The CDC estimates that over 90% of people by this point have been infected." But fortunately, over the past decade, Farhadian and Spudich were already enrolling healthy people from the New Haven community as volunteers to donate blood samples and CSF as research volunteers. Their team was able to use these samples collected before the pandemic as a control.

All participants in the experimental cohort consented to give blood samples and underwent a lumbar puncture to collect CSF. Using these samples, researchers measured levels of inflammatory proteins called cytokines, immune cells, and neopterin, another marker of inflammation. They also evaluated the CSF-to-blood albumin ratio, which indicates blood-brain-barrier integrity.

"We chose these markers because they've previously been found to be elevated in other neuroinflammatory conditions," says Farhadian.

The researchers did not find any significant differences between the experimental and control groups, suggesting that neuroinflammation and blood-brain-barrier dysfunction are unlikely to be the causes of neuropsychiatric symptoms associated with long COVID. Now, the team can turn its attention to other potential causes of long COVID and eventually home in on those that are supported by scientific evidence.

"It's been two years since the pandemic, and it's time to reassess what we know and don't know about long COVID so that we can focus our efforts on finding a solution," says Farhadian. "We were really lucky that our participants were generous in agreeing to enroll in our study."

Ongoing long COVID research will evaluate other possible causes of brain fog

Farhadian and Spudich now plan to focus on other hypotheses that may reveal the biological underpinnings of neuropsychiatric symptoms of long COVID. They will do this by leading translational research conducted through the COVID Mind Study at Yale. Specifically, the team will study whether lingering viral infection of the central nervous system plays a role in symptoms.

Other research led by Lindsay McAlpine, MD, instructor in the division of neurological infections and global neurology and co-author of the neuroinflammation and blood-brain-barrier study, is assessing structural and vascular brain abnormalities.

"We still don't understand what's causing neurological long COVID," says Farhadian. "But our hope is that with more studies, we can start to

eliminate some of the possibilities and zero in on some of the others."

More information: Shelli F. Farhadian et al, Self-Reported Neuropsychiatric Post–COVID-19 Condition and CSF Markers of Neuroinflammation, *JAMA Network Open* (2023). [DOI: 10.1001/jamanetworkopen.2023.42741](https://doi.org/10.1001/jamanetworkopen.2023.42741)

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