

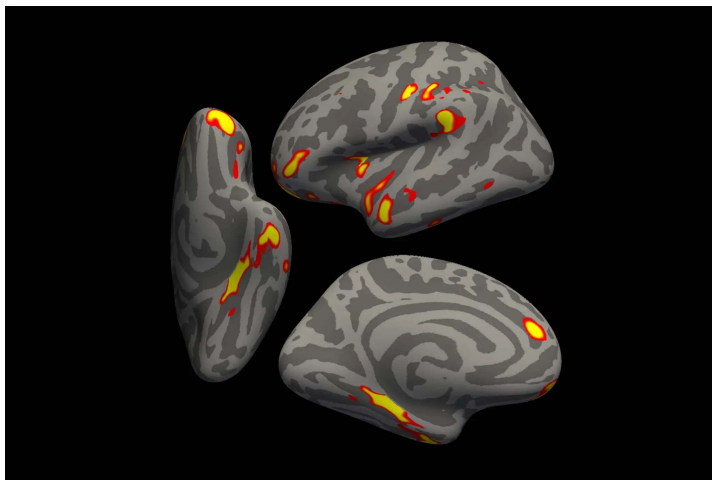
# Covid May Cause Changes in the Brain, New Study Finds

From the *NY Times*, 7 March 2022

*Brain scans before and after infection showed more loss of gray matter and tissue damage, mostly in areas related to smell, in people who had Covid than in those who did not.*

Covid-19 may cause greater loss of gray matter and tissue damage in the brain than naturally occurs in people who have not been infected with the virus, a large new study found.

The study, published Monday in the journal *Nature*, is believed to be the first involving people who underwent brain scans both before they contracted Covid and months after. Neurological experts who were not involved in the research said it was valuable and unique, but they cautioned that the implications of the changes were unclear and did not necessarily suggest that people might have lasting damage or that the changes might profoundly affect thinking, memory or other functions.



A digital model of a human brain showing the parts of the brain that lost the most gray matter in the 401 Covid-infected participants in the study, in red-yellow.

*Credit... G. Douaud, Anderson Winkler and Saad Jbabdi, University of Oxford and NIH*

The study, involving people aged 51 to 81, found shrinkage and tissue damage primarily in brain areas related to sense of smell; some of those areas are also involved in other brain functions, the researchers said.

“To me, this is pretty convincing evidence that something changes in brains of this overall group of people with Covid,” said Dr. Serena Spudich, chief of neurological infections and global neurology at the Yale School of Medicine, who was not involved in the study.

But, she cautioned: “To make a conclusion that this has some long-term clinical implications for the patients I think is a stretch. We don’t want to scare the public and have them think, ‘Oh, this is proof that everyone’s going to have brain damage and not be able to function.’”

The study involved 785 participants in UK Biobank, a repository of medical and other data from about half a million people in Britain. The participants each underwent two brain scans roughly three years apart, plus some basic cognitive testing. In between their two scans, 401 participants tested positive for the coronavirus, all infected between March 2020 and April 2021.

The other 384 participants formed a control group because they had not been infected with the coronavirus and had similar characteristics to the infected patients in areas like age, sex, medical history and socioeconomic status.

With normal aging, people lose a tiny fraction of gray matter each year. For example, in regions related to memory, the typical annual loss is between 0.2 percent and 0.3 percent, the researchers said.

But Covid patients in the study — who underwent their second brain scan an average of four and a half months after their infection — lost more than noninfected participants, experiencing between 0.2 percent and 2 percent additional gray matter loss in different brain regions over the three years between scans. They also lost more overall brain volume and showed more tissue damage in certain areas.

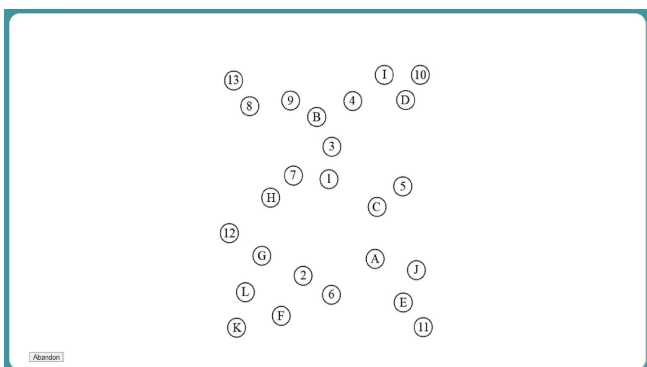
“I find it surprising in the sense of how much more was lost and how generalized it is,” said Dr. Spudich, who has studied the neurological effects of Covid. She added, “I wouldn’t have expected to see quite so much percentage change.”

The effects may be particularly notable because the study involved mostly people who — like the majority of Covid patients in the general population — were mildly affected by their initial Covid infection, not becoming sick enough to need hospitalization.

The study’s lead author, Gwenaëlle Douaud, a professor in the department of clinical neurosciences at the University of Oxford, said that although the number of hospitalized patients in the study, 15, was too small to yield conclusive data, results suggested that their brain atrophy was worse than the mildly afflicted patients.

People who had Covid also showed greater decline than uninfected people on a cognitive test related to attention and efficiency in performing a complex task. But outside experts and Dr. Douaud noted that the cognitive testing was rudimentary, so the study is very limited in what it can say about whether the gray matter loss and tissue damage the Covid patients experienced affected their cognitive skills.

“None of them got thorough enough cognitive testing to know if they had significant deficits in these many regions where they found these changes in volume,” said Dr. Benedict Michael, an associate professor of neurological infections at the University of Liverpool, who is researching the neuropsychiatric effects of Covid and was not involved in the study. “We don’t know that it actually means anything for the patient’s quality of life or function.”



Patients in the study took a trail-making test, a connect-the-dots exercise involving alternating letters and numbers. The Covid patients took longer to complete the task.

For example, although some of the largest gray matter loss was in areas related to smell, including the orbitofrontal cortex and parahippocampal gyrus, those areas are also involved in memory and other functions. But the Covid patients did not perform worse than noninfected participants on memory tests, Dr. Douaud said, although she added that the memory tests they took were brief and basic.

The main cognitive assessment where Covid patients showed a deficit was the trail-making test, a connect-the-dots type of exercise involving alternating letters and numbers. Covid patients took longer to complete the task, which might suggest weaknesses in focus, processing speed and other skills.

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Dr. Douaud said this diminished ability correlated with loss of gray matter in a specific region of the brain’s cerebellum. But the study doesn’t prove cause and effect, said Dr. Spudich, who also said that the cerebellum, primarily associated with balance, coordination and movement, “is not the first brain structure you think of” to explain changes in ability on the trail-making test.

One significant limitation to the study, Dr. Douaud said, is that researchers did not have information about people’s symptoms, including whether they lost their sense of smell. The researchers also could not identify whether any patients had long Covid, so it’s unclear if the findings relate to that long-term condition.

Differences between infected and uninfected people increased with age. On the trail-making test, for example, performance was similar in both groups for people in their 50s and early 60s, but the gap widened significantly after that. “I don’t know if that’s because younger people recover faster or they were not as affected to start with,” Dr. Douaud said. “Could be either or it could be both.”

Dr. Michael cautioned that the findings could not be extrapolated to the many younger people experiencing post-Covid brain fog and other cognitive issues. And since gray matter and tissue damage were measured at only one time-point after infection, “we don’t know if it’s just a transient change that gets better with recovery,” he said.

Outside experts and the study’s authors said the range of brain areas where Covid patients experience more gray matter loss raised intriguing questions.

“There’s no one part of the brain that does one thing,” Dr. Douaud said. “There are parts of the brain in the infected participants with additional gray matter loss that have nothing to do with the smell, and the ones that are related to smell also are involved in other brain functions.”

The cause of the brain changes is unclear. The authors mentioned theories including inflammation, evidence of which has been found in other studies, and “sensory deprivation” from disrupted sense of smell.

Dr. Avindra Nath, chief of the section on infections of the nervous system at the National Institute of Neurological Disorders and Stroke, who was not involved in the study, said another “critical question” was whether the brain changes could make Covid patients more prone to dementia or other deficits in the future.

And while the researchers did not find the same brain changes in patients with non-Covid pneumonia, Dr. Nath recommended studying patients with other coronaviruses or the flu “to see if these findings are distinct for Covid-19 or more generalizable.”

Dr. Spudich said the study’s greatest value may be its indication that “there’s been something that’s happened in the brain in these people,” adding that “I think people have felt that it’s so vague, so hard to measure.”

Other scientists can now build on these findings, she and others said.

“It’s an important study, they’ve done good work,” Dr. Michael said, adding, “now we need to do the studies to look at cognition and psychiatric symptoms and behavioral stuff and neurological stuff and find out what does this mean for patients.”

Here is a link to the original study published in *Nature*

<https://www.bushwalkingholidays.org/pdf/CovidBrainStudyNature.pdf>