Medical News & Perspectives | QUICK UPTAKES

Even Mild COVID-19 May Change the Brain

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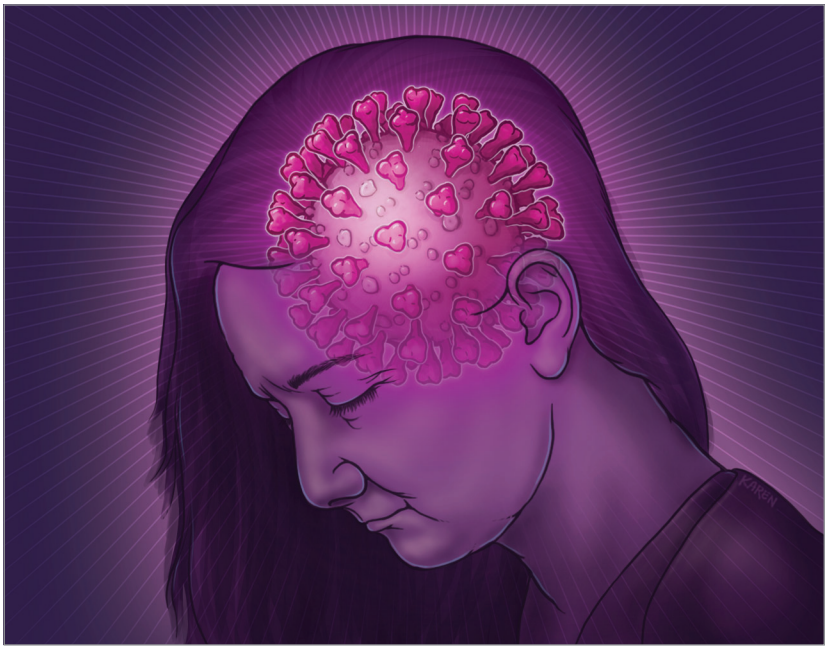
A large study comparing brain scans from the same individuals before and after SARS-CoV-2 infection suggests that brain changes could be a lingering outcome of even mild COVID-19. Writing in *Nature*, researchers at Oxford University's Wellcome Centre for Integrative Neuroimaging reported that several months after study participants had SARS-CoV-2 infections, they had more gray matter loss and tissue abnormalities, mainly in the areas of the brain associated with smell, and more brain size shrinkage than participants who hadn't been infected with the virus.



Why It's Important

Researchers, clinicians, and the public all are eager to learn more about COVID-19's outcomes after the initial infection, especially for individuals with mild or asymptomatic disease, which represents most people with SARS-CoV-2 infection. Of particular interest are brain-related changes that could help explain commonly reported long-term symptoms including loss of smell and taste, headaches, and memory problems.

With nearly 800 volunteers, the new study is the largest COVID-19 brain imaging analyses to date. It's also the first to focus on patients with mostly nonsevere illness and to include preinfection data from the same people. "The fact that we have the pre-infection scan helps us distinguish brain changes related to the infection from differences that may have pre-existed in their brains," Stephen Smith, DPhil, the study's senior author and a professor of biomedical engineering at the Nuffield Department of Clinical Neurosciences (NDCN) at Oxford, said in a statement.

In an email, *JAMA Neurology* Editor S. Andrew Josephson, MD, who was not involved with the work, called the report "an intriguing study that furthers our understanding of COVID-19 and the brain."

The Design

The scans came from the UK Biobank—a research resource with data from half a million volunteers—where Smith is scientific lead for brain imaging. The baseline magnetic resonance imaging took place from 2014 through early March of 2020. For the UK Biobank COVID-19 Repeat Imaging study, the researchers invited hundreds of original volunteers aged 51 to 81 years back for a second round of scans between February and May of 2021. The current reimaging study analysis included:

- 401 cases—volunteers infected with SARS-CoV-2 between March 2020 and April 2021. Of this group, 15 people, or 4%, were hospitalized and 2 received critical care. The group underwent reimaging an average of 3 years after their baseline scans and 4.5 months after their COVID-19 diagnoses.
- 384 controls—volunteers without SARS-CoV-2 infection who were matched with the COVID-19 group for age, sex, ethnicity, the amount of time elapsed between scans, and risk factors such as blood pressure, obesity, smoking, socioeconomic status, and diabetes.

The researchers first estimated brain changes over time in each group and then looked for differences in these changes between the groups. They also compared the groups' changes in cognitive decline based on differences in cognitive task scores. To investigate if other respiratory infections are associated with brain changes, the team compared imaging from separate groups of UK Biobank volunteers who had influenza or pneumonia not related to COVID-19.

What We've Learned

The brain scans and cognitive scores of participants who had been infected with SARS-CoV-2 showed changes between the 2 time points that differed from those seen in the control group, with greater differences among older participants. Although not everyone who became infected with SARS-CoV-2 had these differences, the prior-infection group on average had:

- greater loss of gray matter thickness in the orbitofrontal cortex and parahippocampal gyrus, areas associated with the sense of smell
- greater tissue damage in areas connected with the primary olfactory cortex, also linked with smell
- greater decrease in whole-brain volume and increase in cerebrospinal fluid volume
- greater decline in the ability to perform complex tasks, which on brain scans was associated with atrophy in crus II, an area of the cerebellum associated with cognition

Compared with the control group, volunteers with a prior SARS-CoV-2 infection had an additional 0.2% to 2% gray matter loss or tissue damage on average between their 2 sets of scans. For context, adults lose about 0.2% to 0.3% of gray matter in memory-related brain regions per year, according to Gwenaëlle Douaud, PhD, the study's lead author and an associate professor at the NDCN.

The findings remained statistically significant when the patients hospitalized with COVID-19 were removed from the analysis.

Too few influenza cases occurred to draw comparisons, but brain differences among 11 volunteers who developed non–COVID-19 pneumonia between imaging sessions did not substantially overlap with brain regions implicated in the COVID-19 analysis. This could indicate that the study's findings are specific to SARS-CoV-2 infection, not respiratory infection in general.

Possible Explanations

In their article, Douaud's team offered several potential mechanisms by which SARS-CoV-2 infection might directly or indirectly alter brain structure, including

- reduced sensory input related to loss of smell
- neuroinflammation or immune reactions
- direct viral infection of brain cells

The Limitations

- The volunteers' COVID-19 symptoms were not available to the researchers. They therefore could not connect brain changes with symptoms or with symptomatic vs asymptomatic infection.
- Most participants became infected before COVID-19 vaccines were available in the UK. Some were likely infected by the original SARS-CoV-2 strain but most probably contracted the Alpha variant, according to the authors. How vaccination or different variants such as Delta or Omicron might affect the findings isn't known.
- The study volunteers were predominantly White and were all middle-aged or older adults. It's unknown how the findings will translate to younger adults or to children. The researchers pointed out that the effects were greater in the study's older participants.
- Although the researchers attempted to match the 2 groups as closely as possible, the COVID-19 group at baseline had a subtle pattern of lower cognitive abilities. These differences were not statistically significant and, according to the researchers, could not explain away the study findings.
- The COVID-19 group had structural differences in certain brain regions at baseline compared with the control group, but these regions did not overlap with those that were different in the longitudinal analysis.
- It's possible that the volunteers in the COVID-19 group had subtle preexisting differences from the control group that predisposed them to acquiring SARS-CoV-2 and experiencing its damaging effects.

The Clinical Takeaway

Josephson said the study puts into context concerns about ongoing infections, including those that are mild. But he cautioned that despite the study's cognitive findings, the clinical significance of the COVID-19 group's additional brain changes is not clear.

It's also too soon to know if the changes are reversible. The timeframe between SARS-CoV-2 infection and the second round of imaging was relatively short. "Whether this is a temporary effect, perhaps related to anosmia or inflammation, or an effect that is more long lasting and could be associated with the cognitive and other neurologic and psychiatric changes described in some with long COVID remains an ongoing area of study," noted Josephson, who is a professor and chair of the Department of Neurology at the University of California, San Francisco.

A recent report in *JAMA Neurology* suggests that the cognitive changes observed among some patients with COVID-19 might endure, particularly for those with more severe disease. Investigators found a higher incidence of cognitive impairment among older adults in Wuhan, China, a year after COVID-19 hospitalization compared with their spouses who hadn't been infected, even after adjusting for age, sex, educational level, body mass index, and comorbidities.

On the other hand, in a written FAQ provided to media, Douaud suggested that the damage observed in her team's study might improve in due course: "Since the abnormal changes we see in the brain of the infected participants might be related to their loss of smell, it is possible that recovering their smell might lead to these brain abnormalities becoming less marked over time. Similarly, it is likely that the harmful effects of the virus (whether direct, or indirect via inflammation or immune reaction) decrease over time after infection." She cited small previous studies indicating that issues detected on functional brain imaging may in part improve more than 6 months after SARS-CoV-2 infection.

The bottom line for now, in Josephson's view: "Making sure we are vigilant and attentive to patients' cognitive concerns post-COVID remains extremely important."

Looking Ahead

The findings should be replicated in different populations before being considered definitive. Expect additional analyses from Douaud's group, too. The team hopes to scan the UK Biobank COVID-19 Repeat Imaging study participants for a third time in a year or two.

How best to manage patients' cognitive symptoms remains an area of robust study, according to Josephson. The current analysis, he said, "also emphasizes just how important it is to continue to work to understand the mechanisms of these neurological symptoms and whether vaccination or severity of illness modifies them."

Some of the altered brain regions identified in the study also have memory-related functions. Although there were no signs of memory impairment, if the damage persists, there could be implications for later memory problems or even dementia. Down the line, insight should come from the Alzheimer's Association and researchers from more than 30 countries, who have formed an international consortium to study SARS-CoV-2 infection's effects on the central nervous system in the short- and long-term. ■

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Conflict of Interest Disclosures: Drs Douaud and Josephson reported no disclosures.

Note: Source references are available through embedded hyperlinks in the article text online.