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Covid-19: Studies show lasting cognitive effects after infection

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Two studies published this week have added to a growing body of evidence linking covid infection to subsequent cognitive impairment, even in cases of less severe disease.

One study, a preprint published in *Nature*,¹ examined 785 UK Biobank participants aged 51-81 who routinely receive brain scans and cognitive testing as part of the Biobank's data gathering. About half of the study population, 401 participants, tested positive for covid after such data were gathered. The remaining 384 control participants did not.

In both groups these initial brain scans and cognitive tests were compared with later scans and tests. Participants who had had covid diagnosed showed notably greater changes to the brain, as well as notably greater declines in cognitive scores, than those who did not. This difference remained significant when 15 participants who were admitted to hospital were excluded from the analysis, suggesting that even milder infections are associated with changes to the brain.

The changes seen in the previously infected participants included greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus, greater changes in markers of tissue damage in regions functionally connected to the primary olfactory cortex, and greater reduction in global brain size than was seen in the control group.

Persistent effects

Cognitive scores also declined further over the study period in the infected participants than in the control group. The degree of cognitive decline correlated with the extent of physical changes to participants' brains. The average time from covid diagnosis to the second scan was 141 days, suggesting that negative effects persist for at least four or five months.

"Whether this deleterious impact can be partially reversed, or whether these effects will persist in the long term, remains to be investigated with additional follow-up," the authors wrote.

Rebecca Dewey, a senior research fellow in neuroimaging at the University of Nottingham, who was not involved in the research, praised the study's methodology. "There is a huge advantage from the fact that these people were recruited and scanned before covid was even a thing," she said. "The same people were then scanned at a later date, and so the changes reported use each person as their own control subject, making the findings really strong."

Alastair Noyce, reader in neurology and neuroepidemiology at Queen Mary University of London, called the analysis "robust."

"Some of the most striking results relate to involvement of the parts of the brain concerned with olfaction—sense of smell—which is a recognised symptom of covid," he said. "Earlier studies suggested that covid's effects on smell were outside the brain, but these results indicate possible changes in the olfactory centres in the brain and changes in connected areas."

"I hasten to add that this, as the authors acknowledge, does not mean direct invasion of the brain by covid, and there are several possible explanations. However, it is interesting because a putative mechanism for neurodegenerative diseases is entry via the olfactory structures and then spread to other brain structures."

Wuhan study

The second study, published in *JAMA Neurology*,² followed 1438 covid survivors and 438 uninfected control participants from Wuhan in China, all aged over 60, for a year with cognitive tests at six and 12 months. The study excluded people with pre-existing cognitive impairment, family history of dementia, or serious chronic disease.

Rates of cognitive decline were markedly higher in the infected group, particularly in people who had experienced severe covid. In these participants early onset (mild) cognitive decline was 4.87 times more likely than in the uninfected people (95% confidence interval 3.30 to 7.20), and progressive (severe) cognitive decline was 19 times more likely (9.14 to 39.51). Non-severe covid was associated with a 1.71 times higher risk of early onset cognitive decline (1.30 to 2.27).

"These findings imply that the pandemic may substantially contribute to the world dementia burden in the future," the authors warned.

1 Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 2022 (published online 7 Mar). doi: 10.1038/s41586-022-04569-5

2 Liu Y-H, Chen Y, Wang Q-H, et al. One-year trajectory of cognitive changes in older survivors of covid-19 in Wuhan, China. A longitudinal cohort study. *JAMA Neurol* 2022 (published online 8 Mar). doi: 10.1001/jamaneurol.2022.0461

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