COVID-19

Brain changes after COVID-19 — how concerned should we be?

Stéphane Kremer and H. Rolf Jäger

Analysis of brain images taken before and after infection with SARS-CoV-2 suggests that even mild COVID-19 is associated with brain structure alterations and cognitive impairment. However, the clinical implications for individuals are unclear and further studies are needed to assess the generalizability of the findings and whether the effects are long-lasting.

Refers to Douaud, G. et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* https://doi.org/10.1038/s41586-022-04569-5 (2022).

MRI findings associated with neurological complications of SARS-CoV-2 infection have been well documented in patients who have been admitted to hospital with severe COVID-19. However, most published series have lacked premorbid imaging and have included few patients with mild or subclinical forms of the infection. Recent work published in *Nature* by Douaud et al.[1] fills this important knowledge gap through analysis of brain images taken before and after SARS-CoV-2 infection in patients who experienced mostly mild illness. The results have raised concern, but their full implications remain to be seen.

Douaud et al.[1] analysed longitudinal MRI and neuropsychological data from a total of 785 participants in the UK Biobank. All participants had undergone standardized MRI twice, with an average gap of 3.2 years, as part of the UK Biobank study. However, during the time between MRI procedures, 401 individuals had tested positive for SARS-CoV-2 infection and 384 individuals had not. Consequently, images from before and after SARS-CoV-2 infection were available for all individuals who tested positive, and images from individuals who had not tested positive provided control data. The vast majority (96%) of individuals who tested positive for SARS-CoV-2 did not require hospitalization, and of 15 patients who were hospitalized, only two were admitted to an intensive care unit. Therefore, the study was essentially of the effects of mild SARS-CoV-2 infection.

The investigators performed automated, group-level analysis of volumetric and diffusion-weighted MRI data, using a hypothesis-driven approach (assuming increased vulnerability of the olfactory system) and an exploratory approach. The hypothesis-driven analysis revealed more marked longitudinal cortical volume loss and/or diffusion changes in limbic brain regions functionally connected to the primary olfactory cortex in participants who had tested positive for SARS-CoV-2 infection than in participants who had not. In addition, the exploratory analysis demonstrated that reductions in overall brain size and volume loss in multiple regions were greater among patients who tested positive for SARS-CoV-2. Furthermore, cognitive tests revealed greater decline in executive function among participants who tested positive for SARS-CoV-2 than among those who did not, but no difference in any other neurocognitive domains. The findings are clearly important, but the strengths and weaknesses of the study need to be taken into account to assess its implications.

One major strength of the study is the sample size, which makes it one of the largest brain imaging studies of the effects of SARS-CoV-2 conducted so far. The availability of baseline imaging before infection is also an important strength, and the large control group mitigates the influence that the effects of lockdowns have been shown to have on brain volume[2]. In addition, subgroup analysis after exclusion of the 15 patients who were admitted to hospital produced similar findings, demonstrating that the effects on the brain and cognitive function are apparent even after mild COVID-19.

However, the study has several weaknesses, most of which are discussed by the investigators. In particular, the cohort lacked diversity and consisted of predominantly white (97%) participants aged 51–81 years, meaning that the findings cannot be generalized to other populations and age groups. In addition, the average time interval between MRI procedures (~3 years) is long in comparison with the average time between documented infections and the second MRI procedure (141 days). The relatively long time between MRI studies increases the potential for confounding factors, such as age-related volume loss, to have contributed to the findings, and the short time between infection and the second MRI study precludes assessment of the reversibility of the observed post-infectious changes. Longer-term follow-up studies of patients with COVID-19 suggest that olfaction and cognitive disorders do improve over time[3,4].

The study also has several clinical limitations. First, the baseline characteristics were not perfectly matched between participants who were positive for SARS-CoV-2 and those who were negative. Important differences included slightly poorer performance on initial cognitive testing and smaller baseline thalamic and subcortical volumes among people who subsequently tested positive for SARS-CoV-2 than among control individuals. An influence of these differences on the longitudinal results cannot be excluded. In addition, some clinical information was missing because it was not routinely collected for UK Biobank participants. For example, the SARS-CoV-2 vaccination status of participants was unknown, and no information was available on whether participants experienced gustatory or olfactory symptoms of COVID-19. The latter is highly relevant in the context of the MRI findings in the limbic system and olfactory network.

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The study by Douaud et al.[1] included no investigation of the mechanisms that might lead to the observed brain changes, but the observations do align with one proposed mechanism of CNS involvement in SARS-CoV-2 infection. Three main hypotheses have been proposed to explain this CNS involvement: direct SARS-CoV-2 neuro-invasion; secondary inflammatory processes; and anterograde degeneration that starts with decreased sensory input from olfactory neurons in the nose (olfactory deprivation) and leads to alterations in functionally connected brain regions. These hypotheses are still under debate despite extensive neuropathological studies[5,6], but the third hypothesis would be the most plausible explanation for the increased volume loss and tissue damage in areas directly connected to primary olfactory cortex observed by Douaud et al.[1]. Anosmia is a common symptom of infection with earlier SARS-CoV-2 variants that target ciliated cells of the respiratory mucosa and sustentacular cells[7], and some evidence suggests that direct viral invasion of olfactory

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neurons, the olfactory bulbs and adjacent brain parenchyma is a possible route of CNS entry for the virus[8]. Furthermore, similar brain regions are involved in congenital and other acquired anosmias[9], supporting the hypothesis that anterograde degeneration starts in the olfactory neurons or as a result of olfactory deprivation. Interestingly, olfactory symptoms are also considered as early warning signs in some neurodegenerative disorders. Whether infection with SARS-CoV-2 increases the risk of developing neurodegenerative disorders remains unknown.

The effects on cognitive function observed by Douaud et al.[1] are consistent with other data. Neurocognitive decline, mostly in executive function, after SARS-CoV-2 infection has been observed in up to 81% of patients with severe COVID-19 and up to 40% of patients with mild-to-moderate COVID-19 (REF.[10]). Cognitive impairment and brain volume loss have also been described in other infections that are not associated with olfactory disorders, such as HIV and chronic hepatitis C. In these diseases, direct viral effects have been implicated. For example, HIV crosses the blood–brain barrier via infected monocytes and causes microglial activation. However, direct viral effects seem less likely to have a major role in the neurocognitive effects of SARS-CoV-2 infection, as the virus has not been commonly detected in brain tissue or cerebrospinal fluid.

The main findings of Douaud et al.[1] initially seem concerning, but their full clinical implications are unclear for several reasons. First, the group-level results cannot be extrapolated to individuals, and of note, only 56–62% (depending on the brain region) of people who were infected with SARS-CoV-2 had longitudinal brain volume loss that exceeded the median loss among controls. Second, differences in volume loss of 0.2–2% in various brain regions are relatively small and are not likely to be detectable upon visual assessment of MRI scans of individual patients. Indeed, in our experience, clinical MRI scans of patients with mild SARS-CoV-2 are frequently normal. Third, besides an association between performance on trail-making tests and volume loss in the cognitive lobule crus II of the cerebellum, no associations were observed between volume loss and any other neurocognitive domains, including memory. Fourth, on the basis of the study time frame, SARS-CoV-2 infections among participants were presumably caused by the original SARS-CoV-2 strain or the alpha, beta or gamma variants, so we cannot know whether the findings are applicable to individuals who are infected with the later delta or omicron variants, which cause olfactory symptoms less commonly. Finally, whether similar results can be replicated in adults below the age of 50 years and in non-white ethnic groups remains to be seen.

In summary, this important, large cohort study by Douaud et al.[1] provides evidence of potentially deleterious effects of mild SARS-CoV-2 infection on brain tissue at the group level. However, the limitations of the study make the full clinical implications of these findings unclear. Further analysis of these data, including correlation with vaccination status, olfactory symptoms, and future development of long COVID symptoms, could provide more insight into the vulnerability of particular subgroups. Importantly, additional follow-up imaging is needed to assess the longevity and reversibility of the observed changes.

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Competing interests
The authors declare no competing interests.