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INSIGHT

# Longitudinal Abnormalities in Brain Structure in COVID-19 Patients

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that began in 2019 has been plaguing our life and society [1] and caused untold deaths worldwide. With the proliferation of COVID-19 vaccines and less lethal strains of the virus, the number of patients with severe COVID-19 has gradually decreased. The majority of patients now exhibit only mild-to-moderate symptoms. However, this does not mean that we can let down our guard. Infected patients still suffer not only respiratory distress but also many other comorbidities, especially neuropsychiatric manifestations (Table 1), such as headache, hyposmia/anosmia, impairments in consciousness, anxiety, insomnia, and memory impairment [2–4]. These neurological and neuropsychiatric symptoms may be related to changes in brain structure and function, but direct evidence of these sequelae is still scant.

Previous neuroimaging studies have reported abnormal changes in white matter, the brainstem, and frontal-temporal lobes in COVID-19 patients [5], but cross-sectional design and small sample sizes have compromised the reliability of these results. Douaud *et al.* [6] used the UK Biobank to recruit and investigate brain changes in 785 participants (51–81 years old): 401 COVID-19 patients and 384 controls. They used a longitudinal design and the UK Biobank, which provides neuroimaging data before SARS-CoV-2 infection. A second series of imaging scans was then conducted an average of 141 days after the participants had either medical records that recorded COVID-19 or two positive rapid antibody tests (see Fig. 1 for details). This longitudinal design is beneficial because it excludes preexisting risk factors before infection and verifies that the observed differences resulted from COVID-19 infection. In addition, the strict matching of patients and controls was notably important in their study. Participants in the control group had a negative SARS-CoV-2 test or had no medical record that indicated COVID-19. These controls underwent the same longitudinal imaging experiments. Age, sex, ethnicity, and the time that elapsed between the two scans were also considered. Brain imaging-derived phenotypes (IDPs) and cognitive function at baseline did not differ between groups, further indicating that the brain changes were likely attributable to SARS-CoV-2 infection.

Impairments in olfaction and gustation are common symptoms of COVID-19 [7] and can be used as indicators of the acute phase of infection. The prevalence of smell or taste dysfunction is as high as 68% in infected individuals [8]. This incidence is higher in females, younger patients, and individuals with European ancestry [8]. Although SARS-CoV-2 does not directly target olfactory sensory neurons [9], its infection still results in the downregulation of olfactory receptors [10], which may lead to anosmia. However, most of these studies were performed in rodents or cell lines derived from patients. Remaining unclear is whether there are changes in olfactory-related brain regions in COVID-19 patients. Douaud *et al.* [6] analyzed various IDPs, revealing

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**Table 1.** Possible neurological and psychiatric symptoms in COVID-19 patients.

| Acute neuropsychiatric symptoms after COVID-19 | |
|---|---|
| Psychiatric symptoms | Neurological symptoms |
| Sleep disturbance (e.g., sleep apnea) | Headache |
| Suicidal ideation | Delirium |
| Hallucination | Epilepsy |
| Posttraumatic stress symptoms | Slurring words/speech |
| | Dizziness |
| Post-illness neuropsychiatric presentations associated with COVID-19 | |
| Psychiatric complications | Neurological complications |
| Anxiety disorder | Smell and/or taste dysfunction |
| Mood disorder (depression/bipolar disorder) | Nerve, nerve root, or plexus disorders |
| Posttraumatic stress disorder | Ischemic stroke |
| Substance use disorder | Intracranial hemorrhage |
| Cognitive dysfunction | Dementia |
| Insomnia | Parkinson's disease |
| Memory impairment | Encephalitis |
| | Sensorimotor symptoms |
| | Speech/language issues |

Neuropsychiatric symptoms are wide-ranging. The most commonly reported symptoms include (but are not limited to).

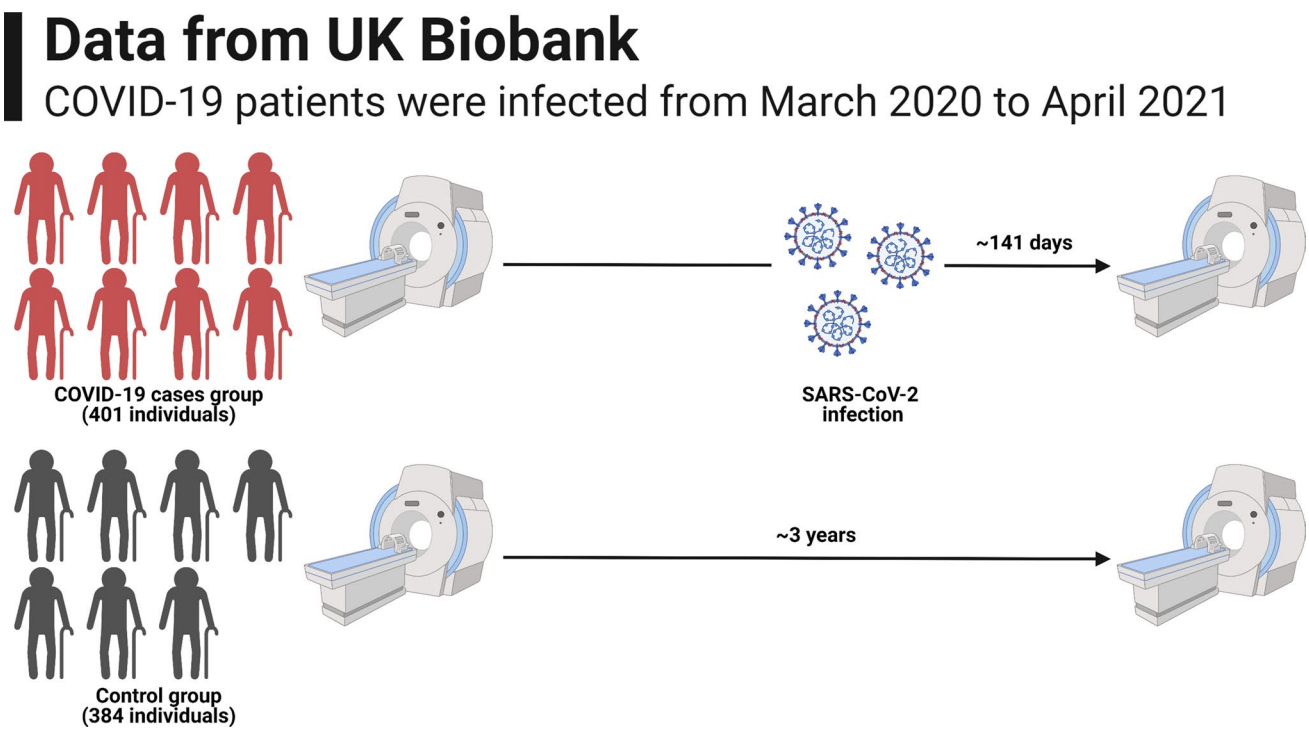


**Fig. 1** Longitudinal neuroimaging study of COVID-19 patients from the UK Biobank. Two imaging scans were performed in 785 UK Biobank participants (401 COVID-19 patients and 384 controls). All individuals were 51–81 years old, an age group that is more vulnerable to SARS-CoV-2 infection. A longitudinal design was used to exclude preexisting risk factors before infection, and a second scan was performed on average 141 days after the COVID-19 diagnosis.

an average 0.7% longitudinal loss in the SARS-CoV-2-positive group compared with controls, covering brain regions that are functionally connected to the primary olfactory cortex, such as the anterior cingulate cortex, orbitofrontal cortex, and insula. Gray matter thickness and volume in the left lateral orbitofrontal cortex and parahippocampal gyrus also decreased over time in the SARS-CoV-2-positive group. Similar results were also found after excluding 15 SARS-CoV-2-positive cases who had been hospitalized. This notable loss of brain volume in COVID-19 patients is abnormal because the longitudinal loss of hippocampal volume only reaches ~0.3% per year in older community-dwelling individuals [11], suggesting that SARS-CoV-2 infection accelerates this aspect of the aging process. The differences between hospitalized and non-hospitalized COVID-19 patients were not significant. However, there was a tendency that hospitalized patients experienced stronger detrimental effects in the orbitofrontal cortex, insula, and parahippocampal and frontal piriform cortex, indicating an association between impairments in olfactory-related brain regions and COVID-19 severity. Notably, these IDPs were specific to COVID-19. No overlap was found with IDPs that were analyzed from patients who suffered from non-COVID-19 pneumonia.

Cognition and memory deficits are also common symptoms in COVID-19 patients. A significant longitudinal decline of cognitive function is evident even 1 year after COVID-19 patients are discharged [12]. Although severe COVID-19 is associated with a higher risk of early- and late-onset cognitive decline, patients who are not severely affected are also at risk of early-onset cognitive abnormalities [12]. Douaud *et al.* [6] applied the trail-making test and found a significant increase in the time to complete Trail A (numeric) and Trail B (alphanumeric) in SARS-CoV-2-positive cases, indicating cognitive impairment in patients with mild-to-moderate COVID-19 (Fig. 2). This cognitive impairment had a significant longitudinal association with a smaller volume of crus II, a cognitive lobule in the cerebellum. In addition, other brain regions that are involved in cognition and memory systems also exhibit abnormalities in COVID-19 patients, such as the parahippocampal gyrus/perirhinal cortex, entorhinal cortex, and hippocampus. This finding may explain the higher risk of Alzheimer's disease and other dementias in SARS-CoV-2-positive cases [13], considering the critical role of the hippocampus in pathologies that are associated with aging and dementia [14].

Many studies [2] have explored the ways in which SARS-CoV-2 invades the central nervous system and have proposed some possibilities, such as cellular transportation and hematogenous transmission. By targeting angiotensin-converting enzyme-2, a docking receptor of SARS-CoV-2

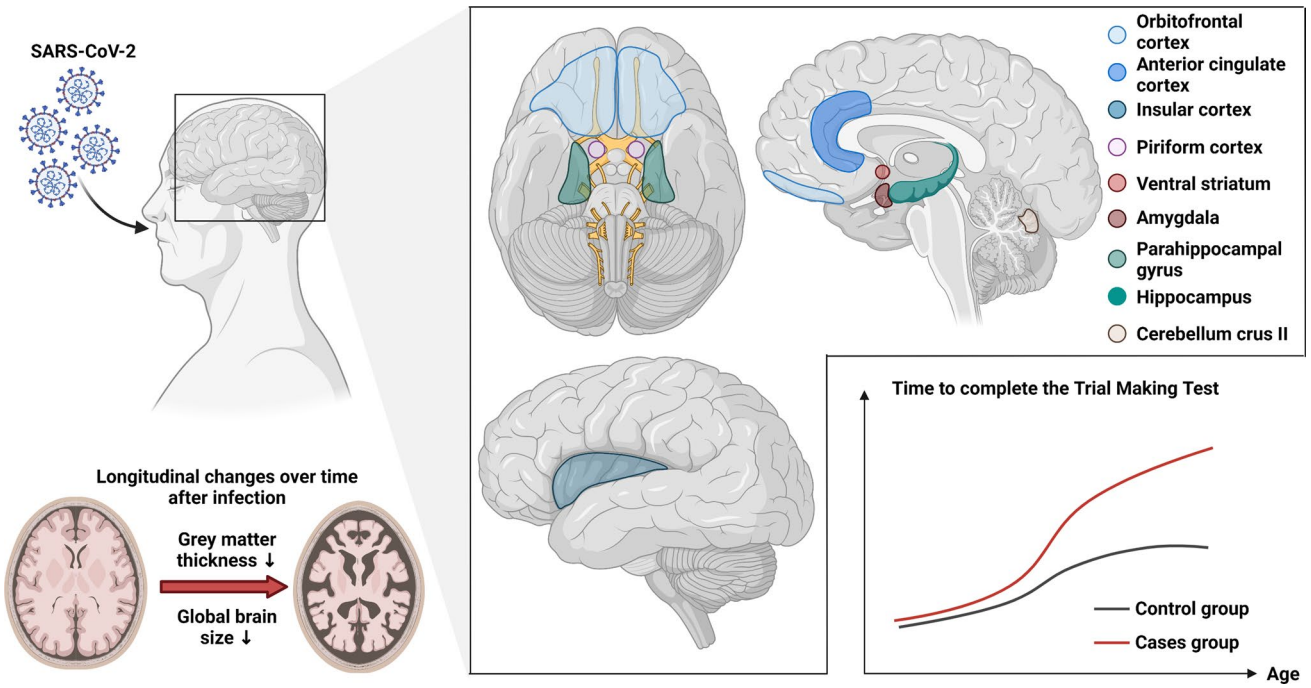


**Fig. 2** Abnormalities of brain structure and cognitive impairment in COVID-19 patients. Compared with the control group, the COVID-19 group exhibited a longitudinal loss of brain volume and a reduction of gray matter thickness in many regions that are functionally connected to the olfactory and cognitive systems, such as the anterior cingulate cortex, orbitofrontal cortex, insula, ventral striatum, amygdala, hippocampus, and parahippocampal gyrus. Atrophy of crus II (a cognitive lobule of the cerebellum) was associated with cognitive dysfunction in SARS-CoV-2-infected individuals.

that is expressed in neurons and glial cells, this virus may trigger a hyperinflammatory syndrome, a pathological cell state, damage of the choroid plexus epithelium, and breakdown of the blood-brain barrier and blood-cerebrospinal fluid barrier [15, 16]. In addition, an abnormal Alzheimer's disease-related pathway is also activated after SARS-CoV-2 infection, especially Tau hyperphosphorylation, which may be a cause for the cognitive defects in COVID-19 patients [17]. Still debatable is whether dysfunction of the nervous system is caused by SARS-CoV-2 replication in the brain or the resulting neuroinflammatory response, such as anti-glial and anti-neuronal autoantibodies [18]. The findings of Douaud *et al.* [6] are a good start for further research on how this virus invades the brain and results in neurological and neuropsychiatric disorders. Further human and animal studies are needed to explore the mechanisms by which SARS-CoV-2 causes brain abnormalities.

Overall, Douaud *et al.* [6] used the UK Biobank to recruit 785 participants, including 401 COVID-19 patients. Using a longitudinal design, they found significant abnormalities in brain regions that are involved in olfactory and cognitive systems, including a loss of gray matter thickness in the left lateral orbitofrontal cortex and parahippocampal gyrus and a smaller volume in the cognitive lobule of the cerebellum (Fig. 2). One limitation of the study by Douaud *et al.* [6] is that subtypes of SARS-CoV-2 were not differentiated in infected patients. Several different SARS-CoV-2 variants have emerged globally, especially the Omicron variant [19] and the new Omicron BA.2 subvariant, indicating a rapid mutation rate of SARS-CoV-2. Considering the different clinical symptoms that are caused by different variants [20], it is unknown whether the imaging results of Douaud *et al.* [6] would be consistent in patients with different variants, which deserves further investigation. In addition, the participants in the study were 51-81 years old, an age group that is more vulnerable to virus infection [21]. They exhibited significant longitudinal loss in some brain regions, especially regions that are functionally connected to the olfactory system. However, disturbances in smell or taste are less frequently reported in COVID-19 patients >46 years old than in younger patients [7, 22]. This syndrome is more prevalent in female patients with SARS-CoV-2 infection [22], thus raising questions about whether the brain changes are sex-specific or age-specific and whether younger infected individuals present more severe brain abnormalities. Future studies should measure brain structure in other more specific age groups, compare brain changes between genders, and attempt to gather imaging data that covers the full life-cycle. The authors also found some abnormalities in brain regions over time, which is consistent with the persistent symptoms in COVID-19 patients. It is unknown whether these changes can be rescued by certain treatments, given that the loss of smell or taste recovers in most infected individuals [23]. Douaud *et al.* [6] did not find this long-term change. Thus, it is critical to conduct follow-up studies to analyze brain structure in COVID-19 patients who do and do not exhibit symptom improvements. Lastly, it is also worthwhile to investigate the brain changes in COVID-19 patients who have received vaccines, so as to further evaluate the protective effect of SARS-CoV-2 vaccination. Altogether, their findings provide novel insights into the impact of SARS-CoV-2 infection on the brain. Future work is needed to further investigate the brain changes in different population with SARS-CoV-2 infection, and more detailed studies are needed to analyze the causes of these abnormalities and their possible treatments.

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