# UK imaging study reveals loss of brain's grey matter in patients infected with COVID-19

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One of the most recognizable features of the COVID-19 infection is the loss of smell and/or taste, disturbances that often precede respiratory symptoms affecting upwards of 80 to 90 percent of those infected. Early in the course of the pandemic, clinicians began to associate the sudden onset of these symptoms without an underlying cause as indications of infection with the SARS-CoV-2 virus.

Additional neurological symptoms include headaches, fatigue, nausea and vomiting in many infected individuals. In severe cases, strokes or impairment in consciousness can occur. Viral neurotropism, a term that describes the ability of viruses to infect nerve tissue, has been hypothesized as possibly the cause for some of these symptoms. Still, evidence for direct invasion by the virus into the central nervous system (CNS) has been limited.

In the course of the pandemic, there has been an intense investigation into the neurotropic ability of the SARS-CoV-2 virus. Given the neurological manifestation of Long COVID symptoms and its impact on cognition, it is critical to understand if the CNS is directly affected by the live virus or if these symptoms are a secondary byproduct of our immune system's response to the infection.

Often, the current literature on this topic is based on only a small series of cases, which can be confounded by a lack of comparisons to uninfected individuals, leading to conflicting results and conclusions. Even many of the neuro-imaging reports published have been performed in people with acute symptoms revealing a broad range of findings but without consistent patterns to elucidate the impact of the infection on the brain in general.

For instance, in an intriguing report published in *Nature* in November 2020, the authors from Charité University of Medicine, Berlin, summarized their findings after conducting a careful postmortem evaluation of the "olfactory mucosa, its nervous projections, and several defined CNS (central nervous system) regions" in 33 individuals, who died from COVID-19. According to the study, one-third had severe neurological symptoms before succumbing to their infections. The olfactory system is the structure that makes up the nose, nasal cavities and the nerves that carry the sense of smell to the regions of the brain where it is perceived.

The authors wrote: "Taken our findings together, we provide evidence that SARS-CoV-2 neuro-invasion can occur at the neural-mucosal interface by trans-mucosal (nasal passages) entry via regional nervous structures. This may be followed by transport along the olfactory tract of the CNS, thus explaining some of the well-documented neurological symptoms in COVID-19, including alterations of smell and taste perceptions."

The olfactory mucosa is situated under a thin strip of perforated bone called the cribriform plate.

The sensory neurons that detect smells are threaded from these holes leading to the brain just above it. Additional study findings included microscopic blood clots in six cases with recently localized infarction of the brain.

Dr. Kiran T. Thakur, a neurologist at Columbia University Irving Medical Center in New York, speaking with the *Washington Post*, explained that the ability of the virus to penetrate deeper into the brain tissue has critical consequences. "A person who has a virus in their brain can have symptoms related to brain involvement. Viruses that invade the brain are tough to eradicate because a barrier protects the brain from the rest of the body. Once viruses enter the brain, the organ can become a refuge for stowaways."

However, countering the findings in the Charité study, he and his colleagues recently published a study that found levels of the actual virus in the brain, compared to the nasal cavities, were very low. This was corroborated by neuropathologist Frank Heppner of Charité, who has studied the brains of over 100 COVID-19 victims. In their not yet published findings, he told the *Post*, "[Our] investigations show low amounts of virus in the brain."

Precisely because there is an urgency for large, well-designed trials to address these questions, the findings of a new UK brain imaging study are fairly important.

Before the onset of the pandemic, UK Biobank, a long-term 30-year study established in 2006 to follow 500,000 volunteers ages 40 to 69 to investigate the contributions from genetics and environmental exposure to disease development, had already conducted 40,000 brain scans. In the context of COVID-19 and its association with the brain, serendipitously, the scientists from the University of Oxford and Imperial College London

invited hundreds of these volunteers to participate in a second imaging visit in 2021 to investigate the correlation.

As the authors noted, this was the first large-scale longitudinal imaging study in COVID-19 patients whose brain scans were compared to before the pandemic and with well-matched controls (for age, sex, ethnic background, and the interval between the two scans) and comparing people who were positive and negative for COVID-19 infection. There were 394 COVID patients and 388 controls. The concluded study was posted on the preprint server medRxiv.

The authors wrote their findings "revealed a significant, deleterious impact of COVID-19 on the olfactory cortex (region of the brain responsible for smell perception) and gustatory cortex (taste and flavor), with a more pronounced reduction in grey matter thickness and volume in the left para-hippocampal gyrus, the left superior insula and the left lateral orbitofrontal cortex in COVID patients." It should be emphasized that this study provided objective evidence of the destructive impact of COVID on the brain.

Grey matter is distributed at the brain's surface, containing most of the brain's neuronal cell bodies and essentially controls all our brain's functions. Besides involving people's sense of smell and taste, the mentioned areas play a role in memory and emotional reactions. The study findings were troubling because the brains of those with mild cases of COVID-19 infection were similar to a small number of hospitalized patients with severe disease, hinting that the impact on the brain is not predicated on the severity of the condition.

The other aspect of the study that makes it compelling is the longitudinal nature with matched controls that assured the researchers that these findings were free of substantial interpretational bias from case studies. However, what remains to be better elucidated is if these findings are a byproduct of a direct infection by the virus or immune/inflammatory changes caused by the disease.

They summarized that "the limbic nature of the regions of the olfactory system, and their physical proximity to the hippocampus, in particular, raise the possibility that longer-term consequences of SARS-CoV-2 infection (for which some suggest that the coronavirus itself enters the brain via the olfactory route) might in time contribute to Alzheimer's disease or other forms of dementia."

The compelling evidence between COVID-19 and the long-term effects on the brain and nervous system led to the initiation in January 2021 of a large international study investigating the correlation between the SARS-CoV-2 virus and the issues behind the cognitive decline, Alzheimer's disease and other dementia that afflict the elderly.

For decades, evidence has been accumulating that respiratory viruses, including coronaviruses, may potentially increase a person's risk for these neurological diseases. Circumstantial evidence for this exists after the Spanish flu. Researchers from almost 40 countries will enroll and follow 40,000 participants aged over 50 who have survived COVID-19 infections to answer these critical questions.

One of the lead authors of the international study, Dr. Gabriel A. de Erausquin from Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases at UT Health San Antonio, explained: "When the trail of the virus, when it invades the brain, leads almost straight to the hippocampus. That is believed to be one of the sources of the cognitive impairment observed in COVID-19 patients. We suspect it may also be part of the reason why there will be an accelerated cognitive decline over time in susceptible individuals."

Given that estimates of the global burden of COVID-19 infections are in the hundreds of millions if not billions, the social and economic implications of the pandemic's impact will be considerable, especially in the decades that will proceed the eventual end of the pandemic.

Dr. Erausquin added: "It really worries me, because if you think that we are already, in developed countries at least, an aging population, and the rate of dementia and diseases of the brain is already likely to increase, the impact of an additional hit on the brain that can accelerate or precipitate the disease without any additional risk factors, that's scary to think about."

The more transmissible Delta variant is well underway to becoming the dominant strain in the US and throughout Europe before the summer's end. In the context of the complete abandonment of all public health measures and school reopenings, school-age children and young adults, who have for the most part still to be vaccinated, face considerable consequences to their long-term neurological health. Most of the planet's population remains naïve (unexposed) to the virus. Should they survive the infection, as most will, how has the criminal response to the pandemic, which continues to place profits over lives and livelihoods, impacted their lives that are still unlived?