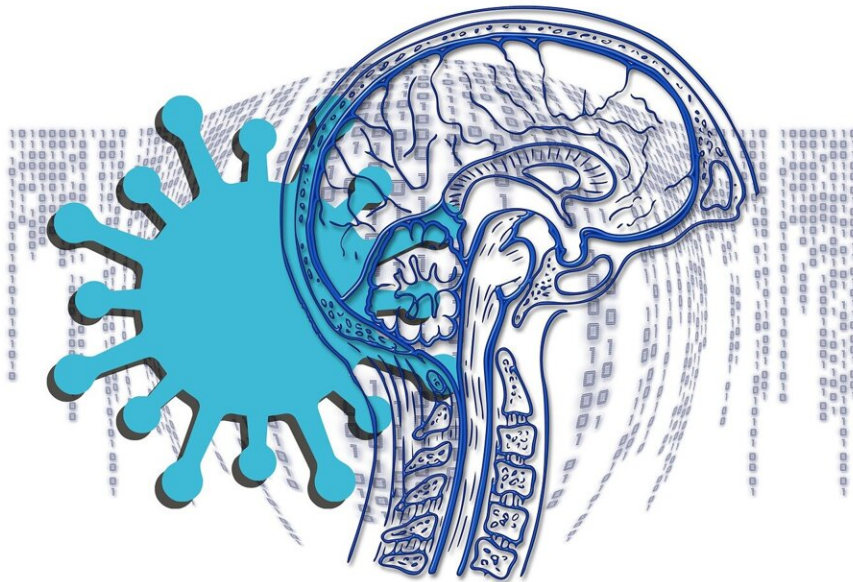


New study reveals possible brain mechanisms behind COVID-19 delirium

October 4 2022



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Researchers from King's College London have shown that when brain cells are directly exposed to blood taken from COVID-19 patients with delirium, there is an increase in cell death and a decrease in the

generation of new brain cells. Delirium represents a state of confusion indicating that, in these patients, the COVID-19 infection had impacted the brain.

The in vitro study provides insight into the possible cellular and [molecular mechanisms](#) involved in the development of [delirium](#) in COVID-19 patients, as well as the general effects of COVID-19 infection on the [brain](#).

Published in *Molecular Psychiatry*, the study's findings indicate a key role for the inflammatory proteins (cytokines) produced by the [immune system](#) during infection, and could help inform potential treatments to reduce symptoms of confusion, disorientation and memory deficits in COVID-19 patients.

Dr. Alessandra Borsini, NIHR Maudsley BRC Senior Research Fellow, Institute of Psychiatry, Psychology & Neuroscience, first author, said, "More and more, research is indicating that there is a neurological element to severe COVID-19 infection, but we have little understanding about what happens in the brain to produce these symptoms. Our research is the first to use [blood samples](#) from COVID-19 patients experiencing delirium to investigate how the infection impacts a process called 'neurogenesis' (the generation of new brain cells), which is essential to maintain intact brain functions, including memory and thought processes.

"We have found that there is a profound reduction in the generation of new brain cells and an increase in [cell death](#), and these are likely mechanisms behind delirium, and possibly other neurological symptoms, in COVID-19 patients."

Previous research indicates that 20 to 30% of COVID-19 patients will develop neurological symptoms such as delirium, with rates of 60 to

70% in cases of severe illness. Delirium is a state of mental confusion that can happen if you become medically unwell and is associated with adverse outcomes, including prolonged hospitalization and death.

Although the respiratory symptoms of COVID-19 are well recognized, the cellular and molecular mechanisms to explain delirium and other neurological symptoms are not well understood. This is the first study to test the direct effect of blood (using serum) taken from hospitalized COVID-19 patients with delirium on the generation of new brain cells in the hippocampus area of the brain.

The development of neurological symptoms in COVID-19 patients is likely to involve an overactive immune response, called the [cytokine storm](#), with an excessive production of these multiple inflammatory proteins. Once produced by the immune cells in the body in response to the infection, these cytokines can then move from the blood to the brain and directly affect brain mechanisms. However, which cytokines are directly relevant to the development of neurological symptoms is currently unknown.

The study collected serum samples from 36 patients admitted to Guy's and St Thomas' NHS Foundation Trust, in London, during the first wave of the COVID-19 pandemic in the UK (March-June 2020). Half of these patients were experiencing delirium symptoms whilst the other half did not present with these symptoms at time of hospital admission.

Researchers used a validated in vitro human cell model that consists of cells from the hippocampus, a part of the brain fundamental in many cognitive, memory and learning skills. Researchers treated cells from the hippocampus directly with the serum samples and observed the impacts on cell generation and death, as well as on the levels of different cytokines.

Results showed that treatment with serum taken from COVID-19 patients with delirium increased cell death and decreased generation of new brain cells. Investigation of the serum showed that those patients with delirium had higher levels of the cytokine IL6, while there was no difference between patients on other cytokines. Treating the brain cells with the serum did produce higher levels of two other cytokines—IL12 and IL13 –suggesting there is a process or cascade where IL12 and I1L3 are generated by brain cells in response to inflammation in the body created by IL6, and together they produce the delirium.

Author Professor Carmine Pariante, Professor of Biological Psychiatry at the Institute of Psychiatry Psychology & Neuroscience (IoPPN), and Consultant Perinatal Psychiatrist at South London and Maudsley NHS Foundation Trust, said, "The role of inflammation and our immune response in COVID-19 infection is well-known, but research like ours is now revealing how it affects our brain, our thinking and our mental health.

"Through a series of tests, we have shown that it is likely that the initial production of cytokine proteins as part of the inflammatory response in COVID-19 infection triggers a cascade of other cytokines which reduce generation of new [brain cells](#) and increase cell death, leading to brain symptoms such as delirium. These [neurological symptoms](#) are very concerning for patients and their families, and the hope is that our research can help identify which treatments would be most appropriate to lessen or prevent these symptoms."

More information: Neurogenesis is disrupted in human hippocampal progenitor cells upon exposure to serum samples from hospitalized COVID-19 patients with neurological symptoms, *Molecular Psychiatry* (2022). [DOI: 10.1038/s41380-022-01741-1](https://doi.org/10.1038/s41380-022-01741-1)

Provided by King's College London

Citation: New study reveals possible brain mechanisms behind COVID-19 delirium (2022, October 4) retrieved 27 April 2024 from <https://medicalxpress.com/news/2022-10-reveals-brain-mechanisms-covid-delirium.html>

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