

Key biological pathway reveals insights into long COVID brain fog

August 16 2023, by Lilly Matson



Credit: CC0 Public Domain

Researchers from University of New South Wales Sydney and St. Vincent's Hospital have identified a key pathway, involved in inflammation, which appears to be activated in people with long COVID

who have symptoms of "brain fog."

Scientists from the School of Psychology and Faculty of Medicine & Health found that of the study cohort of 128 people, those who had a prolonged activation of the [kynurenine pathway](#) were more likely to have mild cognitive deficits 12 months after developing COVID-19. They also found that these symptoms were less likely to improve over time.

Patients who took part in this study had mild to moderate acute COVID-19 and were enrolled in the St Vincent's COVID-19 ADAPT study, a [longitudinal study](#) led by Professor Gail Matthews.

"Together, this study and a previous study in the ADAPT program show that long COVID [brain fog](#) is associated with a dysregulation of the immune response," says Associate Professor Lucette Cysique, lead author of the study. "The current study specifically found that an important metabolic pathway—the kynurenine pathway—is linked to the cognitive changes we're seeing in this group of patients."

The study, published in *Annals of Clinical and Translational Neurology*, helps demonstrate that there is a biological change underlying brain fog in people who have long COVID as a result of mild acute COVID-19 infection.

"I think when patients go to the doctor's with brain fog, it may be dismissed as a psychological problem. Our study speaks to the contrary, that there is a real biological mechanism behind long COVID brain fog," A/Prof. Cysique says.

The discovery opens up possibilities for identifying and treating people who are experiencing the cognitive effects of long COVID and perhaps long COVID in general. "These findings lay the foundation for the kynurenine pathway as a potential diagnostic and monitoring marker, as

well as a possible therapeutic target," A/Prof. Cysique says.

Long COVID and 'brain fog'

Current evidence compiled by the World Health Organization (WHO) suggests approximately 10–20% of people experience a variety of mid and long-term effects after they recover from their initial illness. In fact, up to 100 different symptoms have been recorded as part of the long COVID disease profile.

"Long COVID is a multi-organ disease, so people are differently affected across several of their body functions. This is not surprising as the [immune system](#) is involved across all body functions," says A/Prof. Cysique. "However, we now know that besides fatigue, cognitive changes are the most common symptoms associated with long COVID."

The cognitive dysfunctions experienced by those with long COVID manifest most often as a lack of mental focus or clarity, or mental fatigue that is unusual compared to one's previous capacity, especially after a cognitively demanding task (for example reading complex instructions, participating in a meeting that demands high concentration level, watching a documentary on a topic that is new and complex). This is associated with short-term memory problems, difficulty in multi-tasking or concentration over long periods of time.

As A/Prof. Cysique explains, the best descriptor of brain fog would be a flu-like physical and mental fatigue lasting months, although with some fluctuations.

"With a little introspection, we can all imagine how long-term flu-like physical and mental fatigue would impact everyday function," says A/Prof. Cysique. "And, we are talking of mostly working-age people. Hence, these types of deficits can affect work efficiency to some degree

and probably contribute to the economic impact of the pandemic."

Long-term follow up of COVID patients

While this study included only unvaccinated patients, because the testing was conducted before patients received their first vaccine, the majority of people in the study had long COVID as a result of mild COVID-19 infection. "With vaccination, many of us will still experience mostly mild symptoms. Hence the results are still relevant, especially in the context of reinfection," says A/Prof. Cysique.

As part of A/Prof. Cysique's research, the cohort was followed up at two, four, and 12 months. "At each of these points, the patients went through lots of tests, including on their [mental health](#), [physical health](#) and cognitive health, and patients also had tests for various blood biomarkers on four occasions."

The team decided to investigate the activation of the kynurenine pathway based on [previous experience](#) of studying the pathway in other infectious diseases. In addition, the immune precursor of the kynurenine pathway was shown to be associated with persistent chest and fatigue symptoms in a previous paper [also part of the ADAPT study](#), published in 2022 in *Nature Immunology*.

"While this latest study is a cohort study with factors that remain unmeasured, the convergence of evidence for the importance of the kynurenine pathway in long COVID, and the associated brain fog, is not by chance," says A/Prof. Cysique.

Discovery of an underlying mechanism

A/Prof. Cysique and her team discovered that at two months, when the

kynurenine pathway was the most activated, 60% of those who showed mild cognitive deficits, such as in attention/concentration and speed processing, showed an abnormal activation of the kynurenine pathway—abnormal meaning above the known abnormal level in reference samples of the same age.

"As the immune response takes place, it activates the kynurenine pathway across a period of four months in average—this is much longer than it should be. Because the kynurenine pathway is pro-inflammatory, the entire body, including the brain, is flooded by inflammatory products over a prolonged period. And we know that the kynurenine pathway impacts the central nervous system," says A/Prof. Cysique.

Significantly, no other blood biomarkers, sex, or clinical factors—such as pre-existing or COVID-associated mental health, disease severity or respiratory function, and olfaction—were associated with cognition.

Opening doors to further research

In April 2023, the Australian government announced new research funding for long COVID as a result of the long COVID parliamentary enquiry. It shows that the government recognizes long COVID as a serious issue that demands urgent solutions.

This study has opened the door for further research into potential biomarkers and future therapies for those living with long COVID. "The long COVID clinics are still full of patients and the hospitals are still struggling with the issue," says A/Prof. Cysique. "We hope that our study can provide some hope to people who are suffering from long COVID."

The team are keen to continue building on their research by extending the study cohort to vaccinated patients and to continue the investigation

up to 24 months after the infection date.

"We are also in contact with a Dutch research group who also find that a prolonged activation of the KP is involved in COVID-19 brain changes and want to start a trial," says A/Prof. Cysique.

More information: Lucette A. Cysique et al, The kynurenine pathway relates to post-acute COVID-19 objective cognitive impairment and PASC, *Annals of Clinical and Translational Neurology* (2023). [DOI: 10.1002/acn3.51825](https://doi.org/10.1002/acn3.51825)

Provided by University of New South Wales

Citation: Key biological pathway reveals insights into long COVID brain fog (2023, August 16) retrieved 3 May 2024 from <https://medicalxpress.com/news/2023-08-key-biological-pathway-reveals-insights.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.