How could COVID-19 and the body's immune response affect the brain?

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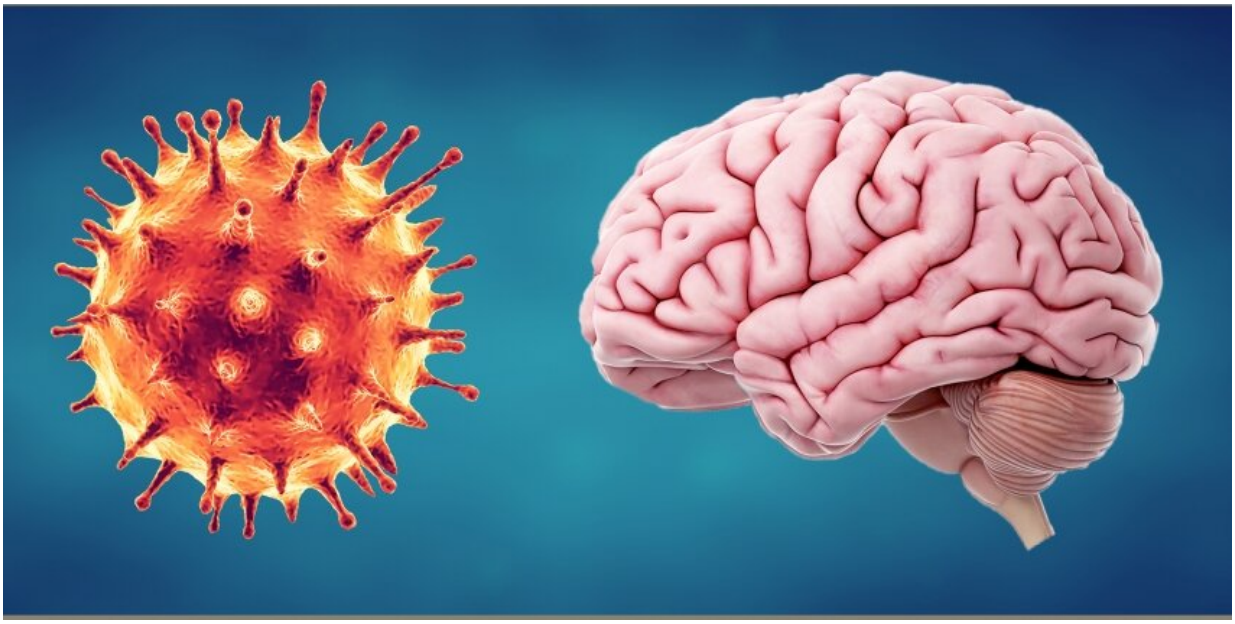

Credit: Picower Institute for Learning and Memory

Although the most immediately threatening symptoms of COVID-19 are respiratory, neuroscientists are intently studying the pandemic from the perspective of the central nervous system. Clinical research and case reports provide mounting evidence of impacts on the brain.

To get ahead of the possible long-term neurological problems from infection, multiple labs in The Picower Institute for Learning and

Memory at MIT have begun pursuing research to determine whether and how it affects the brain, either directly or via the body's heightened immune response. If it indeed does, that would be consistent with a history of reports that infections and immune system activity elsewhere in the body may have long-term impacts on mental health.

While some scientists, for instance, suspect a role for infectious diseases in neurodegenerative disorders such as Parkinson's disease or dementias, Picower Institute Member Gloria Choi and Harvard University immunologist Jun Huh have meticulously traced the pathway by which infection in a pregnant mother can lead to autism-like symptoms in her child and how, counterintuitively, infection in people with some autism spectrum disorders can temporarily mitigate behavioral symptoms. With deep expertise in neuro-immune interactions, as well as in the neural systems underlying the sense of smell, which is reported to be lost in some COVID-19 patients, Choi is planning several collaborative coronavirus studies.

"With these various suspected neurological symptoms, if we can determine the underlying mechanisms by which the immune system affects the nervous system upon the infection with SARS-CoV-2 or related viruses, then the next time the pandemic comes we can be prepared to intervene," says Choi, Samuel A. Goldblith Career Development Assistant Professor of Applied Biology in the Department of Brain and Cognitive Sciences.

Like Choi, Picower Professor Li-Huei Tsai is also planning studies of the neurological impact of COVID-19. Tsai's studies of Alzheimer's disease include investigation of the blood-brain barrier, which tightly gates what goes into and out of the brain through the circulatory system. Technologies that her lab is developing with collaborators including MIT Institute Professor Robert Langer put the team in a unique position to assess whether and how coronavirus infection might overrun or evade

that safeguard.

"It is critical to know how the coronavirus might affect the brain," Tsai says. "We are eager to bring our technology to bear on that question."

Neuro-immune interactions

Choi is considering three lines of coronavirus research. Together with Picower Institute colleagues Newton Professor Mriganka Sur and Assistant Professor Kwanghun Chung, she hopes to tackle the question of anosmia, the loss of smell. Choi has studied the olfactory system in mice since her graduate and postdoc days. Moreover, a key finding of her neuroimmunology research is that because neurons express receptors for some of the signaling molecules, called cytokines, emitted by immune system cells, those interactions can directly affect neural development and activity. Working in mouse models, the team plans to ask whether such an impact, amid the immune system's heightened response to COVID-19, is occurring in the olfactory system.

Based on her and Huh's studies of how maternal infection leads to autism-like symptoms in their offspring, they are concerned about two other aspects of coronavirus infection. One builds on the finding that the risk of offspring developing neurological problems depended strongly on the composition of the pregnant mother's gut microbiome, the populations of bacteria that everyone harbors within their body. Given the wide range of outcomes seen among coronavirus patients, Choi and Huh wonder whether microbiome composition may play a role in addition to factors such as age or underlying health conditions. If that turns out to be the case, then tweaking the microbiome, perhaps with diet or probiotics, could improve outcomes. Working with colleagues in Korea and Japan, they are embarking on studies that will correlate microbiome composition in patients with their coronavirus outcomes.

Over the longer term, Choi and Huh also hope to study whether COVID-19 infection among pregnant mothers presents an elevated risk of their offspring developing neurodevelopmental disorders like autism. In their research in mice, they have showed that given a particular maternal microbiome composition, immune cells in pregnant mice expressed elevated levels of the cytokine IL-17a. The molecule directly influenced fetal brain development, causing neural circuits governing autism-like behavioral symptoms to develop improperly. The pair aim to assess whether that could happen with coronavirus.

COVID-19 access to the brain

A major question is whether and how the SARS-CoV-2 virus can reach the central nervous system. Tsai's lab may be able to find out using an advanced laboratory model of the blood-brain barrier (BBB), whose development has been led by postdoc Joel Blanchard. In a study in press, he has shown that the model made of human astrocytes, brain endothelial cells, and pericytes cultured from induced pluripotent stem cells closely mirrors properties of the natural BBB, such as permeability. In collaboration with Langer, the team is integrating the model with induced pluripotent stem cell-derived cultures of neurons and other crucial brain support cells, like microglia and oligodendrocytes, on a chip (called a "miBrain" chip) to provide a sophisticated and integrated testbed of brain cell and cerebral vascular interaction.

With the miBrain chip platform Tsai's lab plans several experiments to better understand how the virus may put the brain at risk. In one, they can culture miBrain chips from a variety of individuals to see whether the virus is able to permeate the BBB equally or differently in those personalized models. They can also test another means of viral entry into the brain—whether the body's immune system response (a so-called "cytokine storm") increases the BBB's permeability—by using blood serum from COVID-19 patients in the miBrainChip model.

Yet another way the virus might spread in the nervous system is from neuron to neuron via their connections called synapses. With cultures of thousands of neurons, the miBrain chip platform could help them determine whether that's the case, and whether specific kinds of neurons are more susceptible to becoming such conduits.

Finally, there may be genetic differences that increase susceptibility to viral entry to the brain. Using technologies like CRISPR/Cas9, the team can engineer such candidate risk genes into the BBBs to test whether permeability varies. In their Alzheimer's disease research, for example, they study whether variations in a gene called ApoE causes different degrees of amyloid proteins plaque buildup in the BBB model.

The potential interactions among the virus, the microbiome, the immune system, and the central nervous system are likely to be highly complex, but with the expertise, the tools, and strong collaborations, Picower Institute researchers see ways to help illuminate the possible neurological effects of coronavirus infection.

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