

Certain immune reactions to viruses cause learning problems

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HIV infecting a human cell. Credit: NIH

Researchers have discovered a mechanism by which the body's immune

reaction to viruses like influenza and HIV may cause learning and memory problems. This is the finding of a study led by researchers from NYU Langone Medical Center and published online May 15 in *Nature Medicine*.

Evidence in mice suggests that the entry of a virus anywhere in the bloodstream turns on "first responder" immune [cells](#) called CX3CR1^{high}LY6C^{low} monocytes, which then release the inflammatory signaling protein TNF α . According to the authors of the study, TNF α then travels to the [brain](#) where it blocks the formation of [nerve cell connections](#) needed to turn sensory information into memories.

Although immune system activation by viruses has long been linked to cognitive problems, the underlying mechanisms have been poorly understood. In the new report, researchers found that virus-associated immune activation causes a loss of connections between nerve cells within brain circuits in the cortex, the brain region responsible for learning. Such mice then do worse on established tests of learning ability.

The observed changes in nerve connections were triggered, not in the brain, but out in the body (the periphery) where viral infection first makes contact with CX3CR1^{high}LY6C^{low} monocytes in the bloodstream, say the authors.

"This study in animals resonates with what we see in the clinic, where patients with acute or chronic infectious diseases often have weaker performance on motor skills and experience memory decline," says Guang Yang, PhD, assistant professor in the Department of Anesthesiology, Perioperative Care, and Pain Medicine at NYU Langone. "Our results suggest that existing anti-inflammatory treatments that target TNF α may protect against brain dysfunction during peripheral infection."

Fewer Connections

The study results revolve around dendrites, which are offshoots of [nerve cells](#) that pick up electrical signals from the previous cell in a nerve pathway and pass it along. Nerve networks form memories by changing the physical wiring of dendrite branches (spines) to increase the strength of connections (synapses). Previous studies have shown that motor skill learning causes an increase in dendritic spine formation in the motor cortex, and that the extent of new spine formation correlates with the animals' performance improvement as it learns.

In the current study, experiments found that, once exposed to a mimic (mimetic) of viral infection called poly(I:C), mice eliminated more than twice the percentage of dendritic spines as did mice whose immune systems were not activated, suggesting the disruption of synaptic networks.

Furthermore, in mice being trained to run on a rotating rod, which requires muscle coordination (motor) learning, those exposed to poly(I:C) formed significantly fewer dendritic spines.

Researchers also measured the levels of pro-inflammatory signaling proteins (cytokines) in mice at several time points after the injection of poly(I:C), and found a larger, longer-lasting increase in levels of $\text{TNF}\alpha$ than in other cytokines. Given their findings, the team guessed that the impact of systemic immune response on brain cell connections was executed through $\text{TNF}\alpha$ signaling. Indeed, [mice](#) engineered to lack $\text{TNF}\alpha$ signals in white blood cells saw neither a drop in dendritic spine formation nor in motor learning ability when exposed to the viral mimetic.

Moving forward, Guang and colleagues will be looking for drugs or treatments that specifically target $\text{CX3CR1}^{\text{high}}\text{LY6C}^{\text{low}}$ monocytes to

see it they can prevent "undesirable signals to the brain after viral infection." They may also study whether or not existing anti-TNF drugs, such as infliximab, which is used to treat rheumatoid arthritis, could be used to prevent virus-driven cognitive disturbance.

More information: CX3CR1+ monocytes modulate learning and learning-dependent dendritic spine remodeling via TNF- α *Nature Medicine* (2017). [DOI: 10.1038/nm.4340](https://doi.org/10.1038/nm.4340)

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