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Source found for immune system effects on learning, memory

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Immune system cells of the brain, which scavenge pathogens and damaged neurons, are also key players in memory and learning, according to new research by Duke neuroscientists.

Earlier studies by Staci Bilbo, an assistant professor in psychology & neuroscience, had shown that laboratory rats experiencing an infection at an early age have an aggressive immune response to subsequent infections, which also harms their learning and memory.

In a study published in the Oct. 26 *Journal of Neuroscience*, Bilbo's team identifies the source of the learning difficulties and traces it back to the immune system itself.

The researchers found that specialized immune system cells in the brain called microglia release a signaling molecule called Interleukin-1, or IL-1, in response to an infection. IL-1 is also crucial to normal learning and memory in the hippocampus region of the brain. But too much IL-1 can impair learning and memory in laboratory animals.

"These same molecules go up in response to any brain infection. I don't really understand why you would build a brain that way, except that there are clearly benefits in other aspects of immunity, outside the brain," Bilbo said.

In a series of experiments she has been conducting for nearly a decade, very young rats are exposed to infection and then challenged again later

with a second infection consisting of only harmless, dead bacteria. The "second hit" has been shown to affect learning and memory while these rats mount a highly effective immune response.

"The microglia remember that infection and respond differently," she said. "The infection itself wasn't doing permanent damage. It was changing the immune system somehow."

The second infection doesn't even have to be directly involved with the brain. A bacterial lesion on a limb produces enough of a signal to make the glia in the brain pump out extra IL-1. "These rats handle peripheral infection really well, but at a cost to the brain," Bilbo said.

To find out what had changed in the brains of the infected rats, the team used techniques borrowed from immunology to sort out one specific cell type from brain tissue rapidly enough that they could see what the cells had been doing.

The work adds to an emerging picture of glial cells acting in the brain much the same way immune system macrophages operate elsewhere in the body – gobbling up other cells and tearing them apart. The glia also perform a pruning function to streamline the brain's neural architecture as it matures. But some brain disorders appear to be a case of dysfunctional pruning, Bilbo said.

To test how the immune response affected memory, Bilbo's team placed all the rats in a novel environment and exposed them to a sound and a mild shock through their feet. A normal rat remembers the environment after one trial, freezing in place immediately when they enter the familiar setting a second time.

But rats exposed to infection, who tend to overproduce IL-1, stroll through the previously painful experience as if they've never seen it

before, Bilbo said.

Even without experiencing the second immune challenge, the rats infected as youngsters also seem to show cognitive declines earlier than their normal control counterparts. "This is intriguingly similar to what you see in Alzheimer's. It's really kind of scary," Bilbo said.

"These findings could help us understand why some humans are more vulnerable than others to cognitive impairments from chronic infections, aging and neurodegenerative diseases such as Alzheimer's disease," said Raz Yirmiya, a professor of psychobiology at the Hebrew University of Jerusalem, who was not involved in the research. "This might also lead to new approaches toward diagnostic, preventive and therapeutic procedures for these conditions."

Any illness that triggers an immune response tends to slow a person's cognition down as their body enters a recovery mode, but these animals have some sort of permanent change in their immune response, Bilbo said. The newborn rats exposed to infections in these experiments are roughly equivalent to a third-trimester human fetus, but it would be too soon to say what parallels these findings may have in humans, she said.

More information: "Microglia and Memory: Modulation by Early-Life Infection," Lauren L. Williamson, Paige W. Sholar, Rishi S. Mistry, Susan H. Smith and Staci D. Bilbo. Journal of Neuroscience, Oct. 26, 2011. Doi: 10.1523/JNEUROSCI.3688-11.2011

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