March 1, 2021

Neurobiology

Our blood may be making us smarter

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doi.org/10.25250/thescbr.brk483

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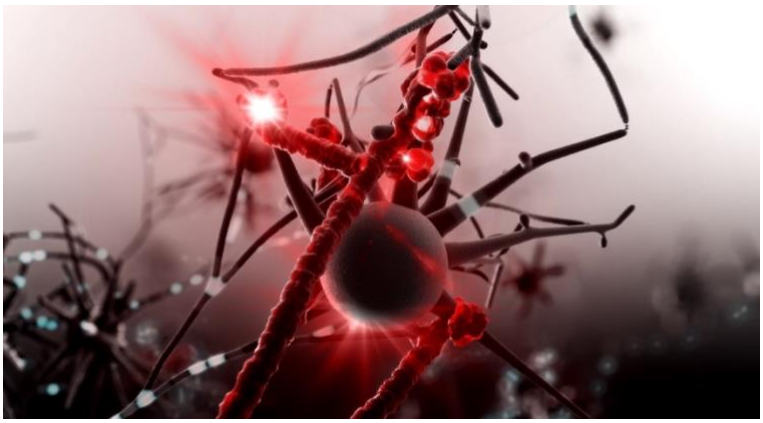
This Break was edited by Ayala Sela, Scientific Editor - TheScienceBreaker

Until recently, the immune system was thought to be excluded from the brain. A new study shows that the immune system is not only able to enter the brain - it must do so if our brains are to reach their full potential. Immune cells in the brain allow neurons to make strong circuits during memory formation. These results identify a new link between the immune system and cognition.



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There is nothing subtle about the immune system. T cells, potent immune cells found in the blood, can kill just about anything. In response to a viral infection, T cells move in, kill any of your cells that have a virus inside them, coordinate a clean-up of the remains and move out. For most organs, this level of collateral damage is acceptable – the cells left alive just reproduce and fill up the missing spaces, and in a few weeks everything is back to normal.

The brain is different. The neurons in the brain form elaborate circuits, linked to each other to create memories and behaviours. If the immune system was to kill neurons, the new neurons would not have the same connections and we would lose memories. To prevent this, we evolved to wall off the brain from the rest of the body, with the blood-brain barrier keeping T cells out. Or so we thought.

Despite the blood-brain barrier, the brain does have its own immune system, of a sort. Microglia are unusual immune cells that enter the brain during early fetal development. If pushed into action by a brain injury or infection they can take on some immune functions of attacking and clearing away cells. However, most of the time microglia are dedicated to supporting learning and memory formation.

The neurons in our brains are highly connected to one another, and contrary to popular conceptions, learning doesn't involve making new connections. Actually, the neurons in the young brain are over-connected, to the point where each individual connection is too weak. To make new memories, neurons need to remove most of their connections so that the ones that are left become a strong circuit. Microglia repurpose their immune functions into a

pruning-like behaviour, where they cut off the unnecessary connections between neurons to allow learning.

We first started investigating the immune system of the brain after several reports of T cells present in brain samples from mice and humans. These reports were initially dismissed as blood contamination, but we started to search for T cells in brains. We could take advantage of the blood-brain barrier by injecting mice with a dye that binds all T cells in the blood stream, prior to looking in the brain. We then looked for T cells in the brain sample that did not come in contact with the dye. Using this approach, we found T cells in the mouse brain, and identified differences between these brain-resident T cells from blood T cells. These differences also allowed us to identify brain-resident T cells in human samples taken during brain surgery.

The next question was whether these T cells in the brain actually did anything! Here we were able to take advantage of mouse strains that had been genetically-modified to not have any T cells. To our surprise, these mice had problems with their microglia. Microglia normally enter the brain during the fetal stage, and gain the ability to prune neurons soon after birth. In mice without T cells, the microglia were present in the brain, but were poor at pruning neurons. This failure to mould the neuronal circuits resulted in mice that had poor memory formation and could not adapt well to new situations. We concluded that microglia needed T cells in the brain in order to carry out their basic functions of supporting neuronal learning!

If mice need an intact immune system to complete brain development and learning, is the same true for humans? We were able to show that both mice and humans had the same population of brain-resident T cells, which expressed the same genes. In theory, the same connection between the immune system and learning could exist in humans. While we can't remove T cells from people for research the way we can with mice, natural "experiments" are occurring all of the time. Cancer patients often lose their T cells as a by-product of chemotherapy, and report short-term memory loss, or "chemo-brain". AIDS patients, who lose their T cells due to HIV attack, frequently suffer from dementia. Children with rare genetic diseases, born without T cells, frequently struggle at school. The data is circumstantial, but suggests there may be a hidden link between the immune system in our blood and the ability of our brain to form memories.