

Important Link between the Brain and Immune System Found

The new line of communication prompts rethinking of neurologic disease

By [Bret Stetka](#) | July 21, 2015

T-cells present in vessels separate from arteries and veins confirm that the brain does in fact have a lymphatic system linking it directly the peripheral immune system.

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When the ancient Egyptians prepared a mummy they would scoop out the brain through the nostrils and throw it away. While other organs were preserved and entombed, the brain was considered separately from the rest of the body, and unnecessary for life or afterlife. Eventually, of course, healers and scientists realized that the three pounds of entangled neurons beneath our crania serve some rather critical functions. Yet even now the brain is often viewed as somewhat divorced from the rest of the body; a neurobiological Oz crewing our bodies and minds from behind the scenes with unique biology and unique pathologies.

Perhaps the most commonly cited division between body and brain concerns the immune system. When exposed to foreign bacteria, viruses, tumors, and transplant tissue, the body stirs up a torrent of immune activity: white blood cells devour invading pathogens and burst compromised cells; antibodies tag outsiders for destruction. Except, that is, in the brain. Thought to be too vulnerable to host an onslaught of angry defensive cells, the brain was assumed to be protected from this immune cascade. However [research](#) published



this month reported a previously unknown line of communication between our brains and immune systems, adding to a fast-growing body of research suggesting that the brain and body are more connected than previously thought. The new work could have important implications for understanding and treating disorders of the brain.

As early as 1921 scientists recognized that the brain is different, immunologically speaking. Outside tissue grafted into most parts of the body often results in immunologic attack; tissue grafted into the central nervous system on the other hand sparks a far less hostile response. Thanks in part to the blood-brain barrier – tightly packed cells lining the brain's vessels that let nutrients slip by, but, for the most part, keep out unwanted invaders like bacteria and viruses – the brain was long considered "immunologically privileged," meaning it can tolerate the introduction of outside pathogens and tissues. The central nervous system was seen as existing separately from the peripheral immune system, left to wield its own less aggressive immune defenses.

The brain's privilege was also considered to be due to its lack of lymphatic drainage. The lymphatic system is our body's third and perhaps least considered set of vessels, the others being arteries and veins. Lymphatic vessels return intracellular fluid to the bloodstream while lymph nodes – stationed periodically along the vessel network – serve as storehouses for immune cells. In most parts of the body, antigens – molecules on pathogens or foreign tissue that alert our immune system to potential threats – are presented to white blood cells in our lymph nodes causing an immune response. But it was assumed that this doesn't occur in the brain given its lack of a lymphatic network, which is why the new findings represent a dogmatic shift in understanding how the brain interacts with the immune system.

Working primarily with mice, lead author and University of Virginia neuroscience professor Dr. Jonathan Kipnis and his group identified a previously undetected network of lymphatic vessels in the meninges – the membranes that surround the brain and spinal cord – that shuttle fluid and immune cells from the cerebrospinal fluid to a group of lymph nodes in the neck, the deep cervical lymph nodes. Kipnis and colleagues had previously shown that a type of white blood cell called T-cells in the meninges are associated with significant influences on cognition and hence were curious about the role of meningeal immunity on

brain function. By mounting whole mouse meninges and using neuroimaging the team noticed that T-cells were present in vessels separate from arteries and veins, confirming that the brain does in fact have a lymphatic system linking it directly to the peripheral immune system. “We stumbled upon these vessels completely by serendipity,” Kipnis commented.

The newly discovered vessels — which were also identified in human samples — could explain a variety of pathophysiological conundrums, namely how the immune system contributes to neurological and psychiatric disease. “It’s early to speculate,” says Kipnis, “but I think that alteration in these vessels may affect disease progression in those neurological disorders with a prominent immune component, such as multiple sclerosis, autism and Alzheimer’s disease.”

For example MS, at least in some cases, is thought to result from autoimmune activity in response to an infection in the central nervous system and cerebrospinal fluid. Perhaps antigens from the infectious culprit find their way to the cervical lymph nodes via the meningeal lymphatic vessels, inciting the immune response that causes MS symptoms. Alzheimer’s is thought to be caused by the build up and transmission of a protein called amyloid in the brain. It could be that the amyloid isn't being cleared properly via these lymphatic vessels, and that somehow improving their patency might help rid the brain of the pathologic protein.

Other recent [work](#) by Kipnis and colleagues found that an injury to the central nervous system results in a strong activation of T-cells in the deep cervical lymph nodes. Kipnis suspects that some compound may be released from the injured CNS that is transmitted to the deep cervical lymph nodes through lymphatic vessels where it activates the immune system. A similar scenario may be at work in other neurological conditions; that too much or too little drainage from the central nervous system to the immune system might contribute to brain disease. If so, Kipnis feels targeting the vessels with drugs, genetic manipulation and surgery are therapeutic approaches worth pursuing.

Dr. Josep Dalmau, a neurology professor at the University of Pennsylvania not involved with the new study, agrees that the new findings could help to explain

the initiation, maintenance, and perhaps worsening of autoimmune disorders that affect the brain; and also that in light of the new findings the textbooks might need some revising “It has become increasingly clear that the [central nervous system] is *immune different* rather than *immune privileged*,” he says. It’s been clear for decades that there is some kind of relationship between the brain and the immune system. Abnormal immune activity was reported in schizophrenia in the 1930s, and numerous mental and neurologic illnesses are known or thought to have an immune component. However that Kipnis’ group identified a tangible, anatomical structure facilitating this relationship suggests that the brain and body are intimately intertwined, and that the brain is not the citadel it was once thought to be.

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