Study details source of mental problems associated with MS

Rochester, NY, USA (January 26, 2016) - A study out today sheds new light on multiple sclerosis (MS), specifically damage in the brain caused by the disease that may explain the role and onset of mental problems that many people experience. The findings, which appear in the Journal of Neuroscience, show that the brain's immune system is responsible for disrupting communication between nerve cells, even in parts of the brain not normally considered to be targets of the disease.

"This study identifies for the first time a new disease mechanism in MS which causes damage to neurons independent of the immune system that wraps the fibers -- or axons -- that connect nerve cells. When myelin is lost or damaged, a process called demyelination, signals between nerve cells can be delayed, disrupted, or even blocked.

Most people associate MS with motor and sensory symptoms like muscle weakness, numbness or tingling in arms and legs, impaired vision, and difficulty with coordination. But about 80% of people with MS also report non-motor symptoms, including problems with memory and concentration. These symptoms can have a profound impact on a person's ability to work, drive, and enjoy life, such as difficulty processing information, concentrating, finding the right word when speaking, and memory loss.

"For too long, MS has been characterized as a disease that impairs people's mobility, speech, or vision," said Harris. "But the evidence from our and other studies suggests that many patients complain has the greatest impact on their quality of life is the loss of cognitive independence."

While physicians currently have at their disposal several frontline drugs that are effective in suppressing the immune system that wraps the fibers -- or axons -- that connect nerve cells, the mechanisms by which these drugs may work have not been fully understood. Previous studies have suggested that neurons that lie outside areas of the brain affected by myelin loss could also be casualties of the autoimmune response in MS patients.

The URMC team conducted a series of experiments in mouse models of MS which showed that neurons in the hippocampus, an area of the brain important in learning, memory, and behavior, can also be damaged by the disease. This damage represents another component of the disease and one that is not prevented by the current immunosuppressive drugs employed to treat MS.

One of the culprits appears to be a cell in the central nervous system's defenses called microglia. Microglia serve as immune sentinels, monitoring the brain for threats and responding to infections by eliminating the cause of the threat.

One of the functions of microglia is to maintain the health of the synapse so that it can function normally to help the brain communicate. However, in the hippocampus, when the disease's immune system causes damage, microglias are activated to help fight infection or other assaults on the nervous system and clean up the debris that results from damage.

"We are activated to help fight infections or other threats to the nervous system and clean up the debris that results from damage," said Harris. "But in the hippocampus, when the disease's immune system causes damage, microglias can also be activated to help fight the disease's immune system and, in doing so, can cause damage to neurons that lie outside areas of the brain affected by myelin loss."

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The microglia release a molecule called platelet-activating factor (PAF) that affects the excitatory signaling that occurs at the synapse. This, in turn, causes more microglia and other immune cells to rush to the site of injury, triggering a chronic and self-perpetuating cycle of destruction. "The cumulative effect is like trying to put out a fire with gasoline," said Gelbard. The researchers believe that this phenomenon is ultimately responsible for much of the cognitive impairment and progressive decline that many individuals with the disease experience.

While the activation of microglia and resulting damage to the synapse is not impacted by the drugs currently used to treat MS, the researchers are studying a potential new treatment to mitigate the ongoing damage that occurs from week to week through a disease-modifying drug that is being developed to treat MS and other neurological diseases.

Additional co-authors of the study include Jasmine Geathers and Kevin Allan with URMC. The research was supported with grants from the National Multiple Sclerosis Society and the National Institute of Mental Health.