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Alzheimer's plaques disrupt brain networks

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Scientist studying the way Alzheimer's takes root in the brain have identified important new similarities between a mouse model and human Alzheimer's.

Researchers at Washington University School of Medicine in St. Louis have shown that brain plaques in mice are associated with disruption of the ability of brain regions to network with each other. This decline parallels earlier results from human studies, suggesting that what scientists learn about Alzheimer's effects on brain networks in the mice will likely be transferable to human disease research.

The study, published in the Journal of Neuroscience, is among the first to precisely quantify the effects of Alzheimer's disease plaques on brain networks in an animal model. Until now, scientists studying Alzheimer's in animals have generally been limited to assessments of structural brain damage and analyses of brain cell activity levels.

"Precise measurement of changes in brain networks are critical to understanding Alzheimer's and will likely be important in models of other neurodegenerative disorders," says senior author David M. Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology. "For example, we can now test whether blocking Alzheimer's plaques from building up in the mouse brain prevents disruptions in brain networks."

In humans, scientists assess the integrity of brain networks by monitoring cerebral blood flow with functional magnetic resonance imaging scans.

When the brain is idle, blood flow rises and falls in sync in brain regions that network with each other, a phenomenon called functional connectivity. These links are believed to be an important component of normal brain activity. In humans, problems in functional connectivity appear to presage the development of dementia.

Applying the same technique to mice can be very challenging, according to Holtzman. Instead, researchers used an approach for monitoring brain blood flow in mice recently developed by the lab of Joseph Culver, PhD, associate professor of radiology at Washington University. The technique involves mounting a ring with light-emitting diodes on the head of a lightly anesthetized mouse. Sensors in the ring monitor light that is reflected back from hemoglobin molecules flowing through blood vessels in the brain. This data can be used to quickly assess blood flow.

Researchers applied the approach to a mouse model of Alzheimer's disease. They found that the brain regions with the strongest network connections in young mice developed the most plaques as the mice aged. As plaques accumulated in these regions, functional connectivity declined. Scientists have already found similar results in humans using functional magnetic resonance imaging.

A link between stronger brain networking in young mice and increased signs of Alzheimer's in older mice may seem contradictory, but it echoes earlier studies in Holtzman's laboratory that linked higher activity levels in individual brain cells to increased plaque deposition.

Holtzman and others have speculated that the types of information and functions encoded in the activities of brain cells and networks may affect their impact on Alzheimer's risk. Epidemiological studies have shown that brain stimulation, such as puzzles, reading or learning, is associated with reduced risk of Alzheimer's. Leaving the brain idle for long periods of time may increase risk.

The mice studied in the research have a mutated form of a human protein, Alzheimer's precursor protein, that causes them to develop brain plaques. Other mouse models have mutated versions of a protein called tau that lead to the development of neurofibrillary tangles, which are another hallmark of Alzheimer's disease.

Holtzman, Culver and colleagues plan to test functional connectivity in mouse models with mutated versions of human tau. The results may help determine the effects of additional types of protein aggregates in the brain, according to Holtzman.

"Important new insights into the normal and dysfunctional human brain have been made via studies of functional connectivity," Holtzman says. "Being able to analyze brain function from a similar perspective in animal models, where we have much more freedom to manipulate genes and proteins, should be very helpful in our efforts to understand and treat complex conditions like Alzheimer's disease."

More information: *Journal of Neuroscience*, March 28, 2012

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