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Alzheimer's risk gene disrupts brain function in healthy older women, but not men

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A team led by investigators at the Stanford University School of Medicine has found that the most common genetic risk factor for Alzheimer's disease disrupts brain function in healthy older women but has little impact on brain function in healthy, older men. Women harboring the gene variant, known to be a potent risk factor for Alzheimer's disease, show brain changes characteristic of the neurodegenerative disorder that can be observed before any outward symptoms manifest.

Both men and women who inherit two copies (one from each parent) of this gene variant, known as ApoE4, are at extremely high risk for Alzheimer's. But the double-barreled ApoE4 combination is uncommon, affecting only about 2 percent of the population, whereas about 15 percent of people carry a single copy of this version of the gene.

The Stanford researchers demonstrated for the first time the existence of a gender distinction among outwardly healthy older people who carry the ApoE4 variant. In this group, women but not men exhibit two telltale characteristics that have been linked to Alzheimer's disease: a signature change in their brain activity, and elevated levels of a protein called tau in their cerebrospinal fluid.

One implication of the study, which will be published June 13 in the *Journal of Neuroscience*, is that men revealed by genetic tests to carry a single copy of ApoE4 shouldn't be assumed to be at elevated risk for Alzheimer's, a syndrome afflicting about 5 million people in the United

States and nearly 30 million worldwide. The new findings also may help explain why more women than men develop this disease, said Michael Greicius, MD, assistant professor of neurology and neurological sciences and medical director of the Stanford Center for Memory Disorders. Most critically, identifying the prominent interaction between ApoE4 and gender opens a host of new experimental avenues that will allow Greicius' team and the field generally to better understand how ApoE4 increases risk for Alzheimer's disease.

For every three women with Alzheimer's disease, only about two men have the neurodegenerative disorder, said Greicius, the study's senior author. (The first author is Jessica Damoiseaux, PhD, a postdoctoral scholar in Greicius' laboratory. They collaborated with colleagues at the University of California-San Francisco and UCLA.) True, women live longer than men do, on average, and old age is by far the greatest risk factor for Alzheimer's, Greicius said. "But the disparity in Alzheimer's risk persists even if you correct for the difference in longevity," he said. "This disparate impact of ApoE4 status on women versus men might account for a big part of the skewed gender ratio."

Besides age, another well-studied major risk factor is genetic: possession of a particular version of the gene known as ApoE. This gene is a recipe for a protein involved in transporting cholesterol into cells — an important job, as cholesterol is a crucial constituent of all cell membranes including those of nerve cells. And nerve cells are constantly responding to experience by developing or enhancing small, bulblike electrochemical contacts to other nerve cells, or diminishing or abolishing them. For all these processes, efficient cholesterol transport is critical.

The ApoE protein comes in three versions, each the product of a slightly differing version of the ApoE gene: E2, E3 or E4. Most people have two copies of the E3 version of ApoE. A small percentage carries one copy

of E3 and one of E2, and even fewer two copies of E2. The protein specified by the E4 gene version seems to be somewhat defective in comparison to the one encoded by either E2 or the much more common E3. Thus, while only about 10-15 percent of the population carries one copy of E4 (or, much less commonly, two), more than 50 percent of people who develop Alzheimer's are E4 carriers.

But, as it turns out, the heightened risk E4 imposes may be largely restricted to women.

To demonstrate this, the scientists first obtained functional MRI scans of 131 healthy people, with a median age of 70, to examine connections in the brain's memory network. They used sophisticated brain-imaging analysis to show that in older women carrying the E4 variant, this network of interconnected brain regions, which normally share a synchronized pattern of activity, exhibit a loss of that synchrony — a pattern typically seen in Alzheimer's patients. In healthy older women (but not men) with at least one E4 allele, activity in a brain area called the precuneus appeared be out of synch with other regions whose firing patterns generally are closely coordinated.

The brain-imaging technique Greicius and his colleagues used is known as functional-connectivity magnetic resonance imaging, or fcMRI. Performed on "resting" subjects, who remain in the scanner awake but not focusing on any particular task, fcMRI can discern on the order of 20 different brain networks, each consisting of a set of dispersed brain regions that are physically connected by nerve tracts and whose pulses of activity are synchronized, or in phase. Greicius, Damoiseaux and their associates have previously shown that the synchronous firing pattern of one network in particular, critical to memory function and known as the "default mode network," is specifically targeted by Alzheimer's and deteriorates as the disease progresses.

To independently confirm their imaging-based observations, the scientists assessed records from a large public database compiled from the Alzheimer's Disease Neuroimaging Initiative, a multi-site study of healthy aging and Alzheimer's disease. The Stanford study focused on the healthy 55- to 90-year-old volunteers who had agreed to undergo a spinal tap and have their cerebrospinal fluid analyzed.

From this database the Greicius team extracted the records of 91 subjects, with an average age of 75, and divided them into four groups representing women with or without a copy of the E4 variant, and men with or without a copy. For each group, they checked recorded concentrations of a protein named tau in these subjects' cerebrospinal fluid. Elevated tau levels in cerebrospinal fluid are a key biomarker of Alzheimer's disease. The results — the CSF of women, but not men, who carried at least one E4 allele was substantially enriched in tau — confirmed the brain-imaging findings.

The tau findings constitute another first. "It was only possible to see these differences in tau levels when we separated the patients by gender," Greicius said.

Notably, all the men and women participating in the Journal of Neuroscience study were screened for cognitive status. Only those whose ability to think and remember appeared normal for their age were admitted. Thus, the observed changes in brain activity and CSF composition were occurring well before the onset of classic Alzheimer's symptoms such as memory loss, disorientation and dementia. It may someday be practical to substitute fcMRI, which is noninvasive, for a spinal tap as a diagnostic tool, Greicius said.

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