Impact of major Alzheimer's-related gene may be felt years before any symptoms appear

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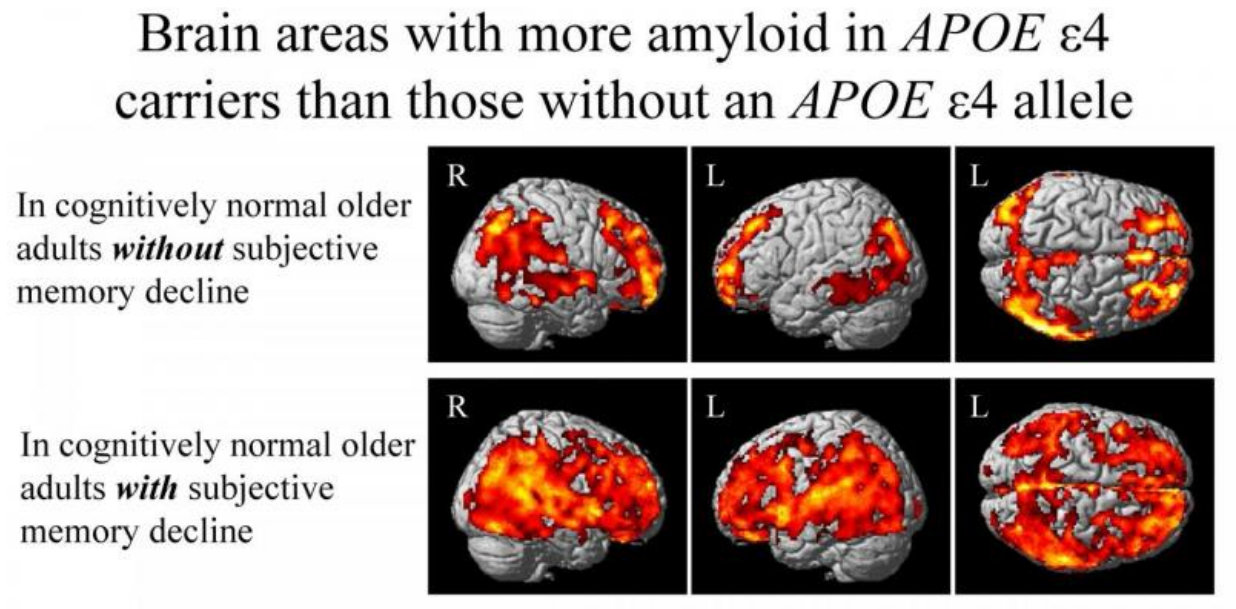

Brain areas with more amyloid in APOE e4 carriers than those without APOE e4 allele, comparing cognitively normal adults with and without subjective memory decline, from research showing may be 'at work' promoting deposits of plaque in the brain long before any symptoms of the disease can be measured on tests Credit: Indiana University School of Medicine

The best-known genetic variant linked to Alzheimer's disease may be "at work" promoting deposits of plaque in the brain long before any

symptoms of the disease can be measured on tests, according to a national research study led by Indiana University School of Medicine investigators.

In a research paper published in the journal *Alzheimer's and Dementia*, the scientists provide additional evidence for focusing research, and eventually treatment, on people at risk of Alzheimer's long before the disease is diagnosed.

The study focused on people with "significant memory concerns," defined as older adults who complained that they had mentally slipped in recent months or years, but when given standard cognition and memory tests they fell within normal ranges. People in this category have also been called the "subjective cognitive decline" group by Alzheimer's researchers.

The paper's authors, led by Shannon L. Risacher, Ph.D., assistant professor of radiology and imaging sciences, and Andrew J. Saykin, Psy.D., director of the Indiana Alzheimer Disease Center and IU Center for Neuroimaging, drew on data collected as part of the national Alzheimer's Disease Neuroimaging Initiative. The ADNI project is a global public-private collaborative initiative that is collecting and making available a broad range of long term Alzheimer's-related data from volunteers ranging from cognitively normal "controls" to patients with diagnosed Alzheimer's disease.

As it becomes more evident that effective treatments for Alzheimer's may need to be applied many years before serious symptoms appear, researchers are focusing more intently on at-risk patients with significant memory concerns, Risacher and Saykin said.

"These are the individuals who are the logical target for the next wave of clinical trials," said Dr. Saykin, who also leads the ADNI Genetics Core.

"There are many potential interventions, and not only on the pharmaceutical side," he said. "There are intensive studies now of exercise, diet modification, cognitive stimulation, sleep and other lifestyle factors that could lead to an improvement."

The gene in question, APOE, has several variants, or "alleles." One of those variants, APOE ε4, has been linked to an increased risk of developing Alzheimer's disease in older adults—although not all Alzheimer's patients have APOE ε4 alleles, and not all those who do will develop Alzheimer's disease. APOE ε4 is common, found in about 25 percent of the population. Patients with Alzheimer's disease who also have APOE ε4 tend to have an earlier age of onset of symptoms.

Looking at data from nearly 600 ADNI participants, the researchers compared those with the APOE ε4 variant to those with other forms of the gene. In the "significant memory concerns" group the researchers found evidence of Alzheimer's-like pathologies from several biomarkers among the APOE ε4 carriers including:

- Increased levels of amyloid plaque, the clumps of protein fragments commonly found in the brain tissue of Alzheimer's patients.
- In the cerebrospinal fluid, decreased levels of the protein precursor to the plaques, suggesting that the protein was being recruited to the brain as part of the plaque creation process.
- In the cerebrospinal fluid, increased levels of tau, another protein associated with Alzheimer's disease.

However, the analysis did not find evidence of reduced levels of glucose metabolism nor atrophy of brain structures that are associated later stages of Alzheimer's progression.

The study provides the foundation for further focused research among

patients at risk of Alzheimer's earlier than in much other research, Dr. Risacher said.

"ADNI provides access to a wide range of biomarkers, structural and functional neuroimaging with MRI, PET scans for amyloid and for glucose metabolism, CSF biomarkers for amyloid and tau, plus genetics, and clinical and cognitive tests. No other data set has all these state-of-the-art biomarkers available for analysis," she said.

Provided by Indiana University