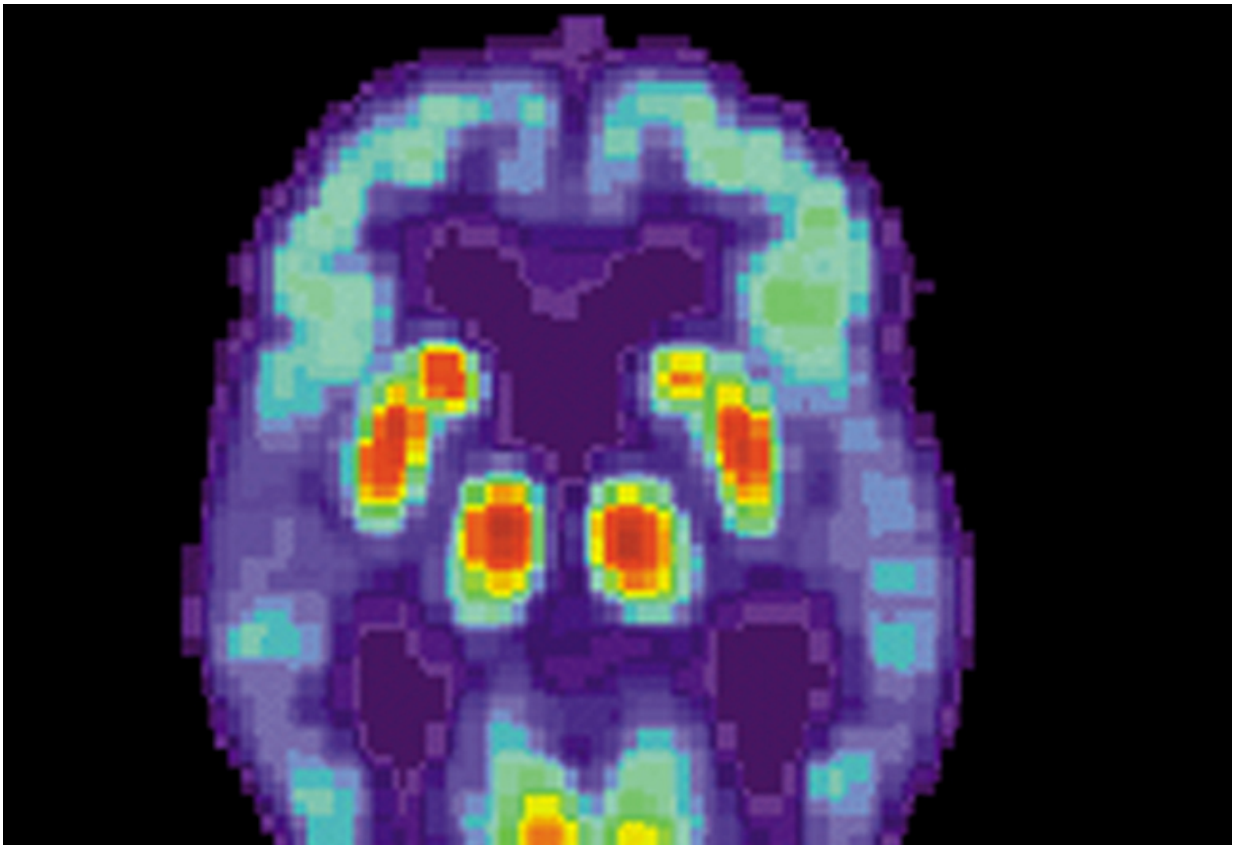
Inflammatory proteins may slow cognitive decline in aging adults

June 23 2021



PET scan of a human brain with Alzheimer's disease. Credit: public domain

Research has previously linked inflammation to Alzheimer's disease (AD), yet scientists from Massachusetts General Hospital (MGH) and the Harvard Aging Brain Study (HABS) have made a surprising

discovery about that relationship. In a new study published in *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, they report that elevated levels of two chemical mediators of inflammation, known as cytokines, are associated with slower cognitive decline in aging adults.

"These are totally unexpected results," says the study's co-senior author, Rudolph Tanzi, Ph.D., vice chair of Neurology and co-director of the Henry and Allison McCance Center for Brain Health at MGH. These findings could eventually be used to help identify healthy people who are at risk for the devastating neurological condition, before they have symptoms.

In 2008, Tanzi led a team that discovered CD33, the first AD gene associated with the immune system (or the body's defense network that fights infection). Since then, most new AD genes identified have been linked to the immune system, and many studies support the theory that immune system dysfunction plays a part in AD. Notably, research has shown that people with AD and other forms of dementia have elevated levels of certain cytokines.

However, until now the role of the immune system in the earliest stage of AD—when brain changes characteristic of the disease silently progress in older adults without cognitive symptoms—was unclear. In the new study, Tanzi and his team collaborated with HABS investigators to find out if measuring cytokines in the blood (instead of in cerebrospinal fluid, which requires a lumbar puncture procedure, or spinal tap) could help predict which healthy people will later experience cognitive decline. Of particular interest were older people with normal cognition, but who had undergone imaging tests and were found to have deposits of amyloid beta—the major component of amyloid plaques, which are associated with AD—in their brains. "We wanted to know why some people have amyloid in their brain and don't seem to be affected, while other people experience cognitive decline," says study co-

senior author Jasmeer Chhatwal, MD, Ph.D., a neurologist at MGH and a HABS co-investigator.

The partnership between the McCance Center and HABS, which is co-led by Reisa Sperling, MD, and Keith Johnson, MD, "was a natural fit," says Chhatwal, since both groups seek to understand the secrets of healthy aging and identify biomarkers of brain health. Moreover, HABS had rich data to examine. The new study included 298 men and women from HABS, who were between the ages 50 and 90. All had normal cognitive abilities when they volunteered and undergo retesting annually. Upon joining HABS, all participants had blood samples taken and underwent positron emission tomography (PET) brain-imaging scans; among other things, these scans looked for evidence of amyloid beta and other changes associated with AD, such as formations called tau tangles.

The study screened each participant's blood for nine cytokines to see if any were associated with the rate of cognitive decline and changes in the brain. The study found that people whose brains had a significant burden of amyloid beta, but who also had high levels of a pro-inflammatory cytokine called interleukin-12 (IL-12), experienced little cognitive decline. "However, men and women with elevated levels of amyloid declined more if they had a lower value of IL-12," says lead author Hyun-Sik Yang, MD, a neurologist at Brigham and Women's Hospital and a HABS co-investigator. High levels of IL-12 were also associated with fewer tau tangles. Meanwhile, elevated levels of another pro-inflammatory cytokine, interferon-gamma (IFN-γ), were associated with slower cognitive decline, whether or not a person had deposits of amyloid.

While it may seem counterintuitive that people who were protected against cognitive decline had the highest levels of inflammation-inducing proteins in the blood, that may be an indication that their immune systems were better "primed" to fight infection, says Tanzi. That would

fit with a theory he developed with the late Robert Moir, Ph.D., a researcher at MGH and Harvard University, in which they hypothesized that amyloid beta forms in the brain as a defense against infection, ensnaring microbial pathogens in a sticky web. Unfortunately, the once-protective shield turns destructive over time, causing irreversible damage to neurons and synapses. However, having high levels of IL-12 and IFN-γ "may nip infections in the bud, before they can leak into the brain and induce Alzheimer's pathology," says Tanzi.

These results suggest that IL-12 and IFN-γ could one day be measured along with other biomarkers to predict future brain health in cognitively normal people—a tool that doesn't yet exist in medicine. "We don't have a 'checkup from the neck up'," says Tanzi. The next step toward that goal will be studying how IL-12 and IFN-γ may ward off cognitive decline and promote healthy brain aging.

Tanzi is the Vice-Chair of Neurology (Research) and Co-Director of the Henry and Allison McCance Center for Brain Health at MGH, and the Joseph P. and Rose F. Kennedy Professor of Neurology at Harvard Medical School (HMS). Chhatwal is an assistant professor of Neurology at HMS. Yang is an assistant professor of Neurology at HMS.

More information: Hyun-Sik Yang et al, Plasma IL-12/IFN-γ axis predicts cognitive trajectories in cognitively unimpaired older adults, *Alzheimer's & Dementia* (2021). DOI: 10.1002/alz.12399

Provided by Massachusetts General Hospital