What comes first, beta-amyloid plaques or thinking and memory problems?

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The scientific community has long believed that beta-amyloid, a protein that can clump together and form sticky plaques in the brain, is the first sign of Alzheimer's disease. Beta-amyloid then leads to other brain changes including neurodegeneration and eventually to thinking and memory problems. But a new study challenges that theory. The study

suggests that subtle thinking and memory differences may come before, or happen alongside, the development of amyloid plaques that can be detected in the brain. The study is published in the December 30, 2019, online issue of *Neurology*, the medical journal of the American Academy of Neurology.

"Our research was able to detect subtle thinking and memory differences in study participants and these participants had faster amyloid accumulation on brain scans over time, suggesting that amyloid may not necessarily come first in the Alzheimer's disease process," said study author Kelsey R. Thomas, Ph.D., of the VA San Diego Healthcare System in San Diego. "Much of the research exploring possible treatments for Alzheimer's disease has focused on targeting amyloid. But based on our findings, perhaps that focus needs to shift to other possible targets."

The study involved 747 people with an average age of 72. Researchers gave participants neuropsychological tests at the beginning of the study and measured their total scores and also their process scores to determine if they had subtle thinking and memory difficulties. What is a process score? While a person may score within the normal range on thinking and memory tests, process scores reflect how that person solves problems, measuring errors in their approach to completing tasks.

Looking at both total scores and process scores, researchers divided participants into three groups: 305 people with normal thinking and memory skills; 153 with subtle thinking and memory differences; and 289 people with mild cognitive impairment.

Participants had brain scans at the start of the study to determine levels of amyloid plaques in the brain, and then yearly scans for four years.

After adjusting for age, education, sex, genetic risk for Alzheimer's

disease, and amyloid level at the start of the study, researchers found people with subtle thinking and memory differences had a more rapid accumulation of amyloid compared to people with normal thinking and memory skills. On a test that uses a dye to measure amyloid levels, where the average level was 1.16 for participants with subtle thinking and memory difficulties, amyloid levels in this group increased by .03 above and beyond the amyloid changes in those with normal thinking and memory skills over four years. People with subtle differences also had faster thinning of the entorhinal cortex, a brain region that is impacted very early in Alzheimer's disease.

On the other hand, researchers also found that, while people with mild cognitive impairment had more amyloid in their brains at the beginning of the study, they did not have faster accumulation of amyloid when compared to those with normal thinking and memory skills. However, they did have faster thinning of the entorhinal cortex as well as brain shrinkage of the hippocampus.

"From prior research, we know that another biomarker of Alzheimer's disease, a protein called tau, shows a consistent relationship with thinking and memory symptoms. Therefore, more research is needed to determine if tau is already present in the brain when subtle thinking and memory differences begin to appear," said Thomas.

"Finally, our study demonstrated a method to successfully detect subtle differences in thinking and memory either before or during the phase when amyloid is accumulating at a faster rate," Thomas said. "This could lead to non-invasive screenings that may be able to detect very early who is at risk of developing Alzheimer's disease."

A limitation of the study was that participants were mostly white and considered healthy, so the results may not be the same for other populations. It is also possible that the earliest stages of amyloid plaques

forming in the brain are not detectable with brain scans.

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