

100-year-olds with signs of Alzheimer's in the brain are still sharp

Amyloid plaques and tau tangles tend to accumulate in the brain as we get older, but at the most advanced ages they don't correlate with cognitive symptoms

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Brain scans that show signs of Alzheimer's disease

MRI scans showing changes in the brain associated with Alzheimer's disease

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For people who live to 100 or beyond, changes in the brain usually associated with Alzheimer's disease don't seem to correlate with cognitive impairment.

For decades, researchers have suspected that clumps of proteins known as amyloid plaques and tau tangles were the main drivers of [Alzheimer's disease](#) because they are found in the brains of people who die from the condition.

Yet a growing pile of evidence has also shown that many people who live into their ...

mid-70s and beyond [don't show signs of cognitive impairment](#) despite having these protein clumps in their brains.

This raises questions about the role of these brain changes, including whether people who have them but show no signs of cognitive decline are somehow resilient to Alzheimer's disease or if the build-up of plaques is a result of another process and not a driving cause of Alzheimer's.

To investigate this further, [Henne Holstege](#) at Vrije University Amsterdam Medical Center in the Netherlands and her colleagues assessed the brains of 2131 people who died between the ages of 16 and 103. In this group, 851 had been diagnosed with Alzheimer's disease, 626 had had another form of dementia and 654 had shown no signs of cognitive impairment.

They then evaluated each brain for three hallmarks of Alzheimer's disease: amyloid plaques, tau tangles and neuritic plaques, which are clumps of amyloid plaques surrounded by degenerating, tau-containing neurons. Using standard grading criteria, they rated the severity of amyloid plaques on a scale of 0 to 3 and tau tangles on a scale of 0 to 6, with higher numbers indicating greater severity.

They found that, as people age, the amount of amyloid and tau steadily rises, even in the absence of Alzheimer's symptoms. At age 60, for example, average amyloid scores were 2.5 points higher in people with Alzheimer's disease than in people without dementia. But by around age 95, the difference in scores had narrowed to 1.5. For tau, the difference in average scores between the two groups decreased from around 6 at age 55 to around 2 by age 95.

At age 50 or 60, the presence of amyloid plaques and tau tangles indicates there is something wrong with the brain, says Holstege. "But that's not true for people who have reached really old ages," she says.

It is a different story with neuritic plaques, however. The researchers rated them on a scale of 0 to 3, with 3 being the most severe. They found that the difference in average scores between people with Alzheimer's and those without dementia remained higher than 2, even past 90 years old. "Neuritic plaques are something that we really don't want. That's a sign of pathology," says Holstege.

The researchers also examined the brains of 85 [centenarians](#) who died between the ages of 100 and 111. They were part of the 100-plus cohort, an ongoing medical research initiative in the Netherlands. Participants had no signs of cognitive impairment when they joined the

study and completed yearly assessments using a test that rates cognition on a scale of 0 to 30, with scores of 25 or higher indicating normal functioning.

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On average, centenarians had a cognitive score of 25 at their last test despite showing brain changes associated with Alzheimer's: the average amyloid score for the group was 2, tau score was 3 and neuritic plaque score was 1. While these scores are better than those of people in the comparison group diagnosed with Alzheimer's, they are the same or worse than those of older people in the comparison group without signs of cognitive impairment: people aged 90 and older who showed no Alzheimer's symptoms had an average amyloid score of 2, tau score of 2 and neuritic plaque score of 0.

These findings suggest that these protein clumps continue to accumulate in the brain as people age – but at very advanced ages they don't correlate with cognitive ability.

That was particularly pronounced in a handful of cases: five centenarians with the highest amyloid score, three with the second-highest tau score and two with the highest neuritic plaque score all had a cognitive score of 25 or more.

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“You're seeing plaques, you're seeing tangles and you're not seeing the amount of dementia you would expect,” says [Rudolph Tanzi](#) at Massachusetts General Hospital in Boston, who wasn't involved in the study. “The question is, how does one brain tolerate it and another does not?”

One possible explanation, he says, is a lack of neuroinflammation. In Alzheimer's, immune cells in the brain called [microglia](#) attack these plaques, causing inflammation that can kill neurons. This response may not occur in centenarians, possibly because they have different variations in genes related to microglial function, which have previously been implicated in Alzheimer's disease, he says.

“We can learn so much from folks who develop age-related brain pathology but somehow escape dementia and live a long time,” says Tanzi. “Because then you can develop drugs and therapies that mimic that.”

Reference: medRxiv, DOI: [10.1101/2022.08.28.22279304](https://doi.org/10.1101/2022.08.28.22279304)

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