

# New insights into why women develop Alzheimer's symptoms earlier and exhibit faster memory decline

*Reviewed by Emily Henderson, B.Sc. Feb 16 2022*

A joint study by Nanyang Technological University, Singapore (NTU Singapore) and National University of Singapore (NUS) scientists has examined why, in mice, female brains are more predisposed to Alzheimer's disease and other neurodegenerative diseases.

Alzheimer's is the world's most common neurodegenerative disease, affecting the memory, thinking and behaviour of over 40 million people worldwide. It accounts for 60 to 70 per cent of dementia cases and is known to affect more women than men.

The study sought to provide insights why women developed Alzheimer's-related symptoms earlier and exhibited a faster decline in memory compared to men. By experimenting on mice brain samples, the research team found that as female mice age, they experienced a faster decay in their information processing ability compared to male mice, resulting in weaker memory formation and increased memory loss.

The study, led by Assistant Professor Ch'ng Toh Hean from NTU's Lee Kong Chian School of Medicine and Associate Professor Sajikumar Sreedharan from the NUS Yong Loo Lin School of Medicine's Department of Physiology, showed that the brains of female mice with the Alzheimer's genetic mutation were less flexible, or "plastic", in adapting to new information and forming new memories.

This lowered plasticity of the brain's synapses - the connections between brain cells, or neurons - likely contributes to greater cognitive impairment and increased vulnerability to Alzheimer's disease in females, say the scientists.

*It is well-documented that Alzheimer's disproportionately affects more women than men, with women at a higher risk of developing the disease. For a long time, scientists have thought that this discrepancy was because women on average live longer than men, but our study based on mice models provided evidence that the processing time of information in female brain synapses declines much earlier compared to male brain synapses."*

*Ch'ng Toh Hean, Assistant Professor, NTU's Lee Kong Chian School of Medicine*

"More recent studies suggest that there are biological reasons beyond longevity that explains the sex discrepancy, such as genetics, hormones, and lifestyle impact. However, although the associated risk factors are clear, the exact reasons why female brains show this faster decline - and are hence more susceptible to Alzheimer's - require further study," he said.

The findings were published in *Aging Cell* in November 2021. The joint study was funded by a Singapore Ministry of Education Academic Research Fund Tier 3 and the NTU Nanyang Assistant Professorship and supported by the NUS Joint Research Programme (NUSMED-FOS).

How Alzheimer's affects brains of different sexes

The research team, which includes NTU research fellows Dr Sheeja Navakkode and Dr Jessica Gaunt, sought to identify some of the molecular mechanisms in memory formation and the progression of Alzheimer's disease between both sexes.

Alzheimer's disease is a progressive neurodegenerative disorder that results in the loss of neurons and their connections. It is the most common cause of dementia and is characterised by decline in memory. As the disease progresses, patients develop severe memory impairment together with decline in behavioural and social skills.

The team's lab experiments revealed that female mice with mutations associated with Alzheimer's disease had a faster decline in long-term potentiation (LTP) compared to the mutant male mice. LTP in the hippocampus is the process by which synaptic strength is increased between neurons that form long-term memories, making it one of the major cellular mechanisms guiding how the brain forms memories and learns new things.

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The scientists stimulated mice brain samples which have Alzheimer's mutations using electricity and recorded the resulting brain waves and activity. In a series of experiments, the scientists showed that the memory formation through LTP tends to decay faster in female mice bred to be more susceptible to Alzheimer's compared to males.

"In the model, if LTP remains strong over a long period of time, it indicates that a memory is stable," said Asst Prof Ch'ng. "If it decays over time, then the memory is lost. The correlation we drew here is that by seeing rapid decay in LTP, the memory is corrupted and weakened, much like what happens in an Alzheimer's patient."

In one experiment, the scientists induced LTP in mice using strong tetanic stimulation (STET) - a high-frequency burst that stimulates the brain's neurons. They found that a STET-induced LTP lasted for 180 minutes in Alzheimer-susceptible males, but only 95 minutes in females. Similarly, a theta burst stimulation-induced LTP lasted 90 minutes in male mice, and 70 minutes for female mice.

"The findings from different tests shows faster LTP decline in female mice lends credence to the idea that there is strong robust difference between the sexes," said Asst Prof Ch'ng.

### Faster memory decline in female brains

Analysis of brain sections also showed that female mice with Alzheimer's disease have increased markers of inflammation, which could explain why there is greater deterioration of LTP in female mice.

NTU senior research fellow Dr Sheeja Navakkode, the paper's first author, said: "Our results showed that a stronger inflammatory response, coupled with weaker plasticity in the hippocampus of Alzheimer's disease females, could explain why there is faster memory decline in Alzheimer's females compared with males."

"Studying Alzheimer's in genetically modified mice is useful as they model different aspects of the disease. This is particularly true when investigating cell and molecular pathways in the brain that are similar in humans and mice," she added.

Asst Prof Ch'ng said: "As diminished synaptic function is an early event of Alzheimer's disease, strategies to detect early decay of memory may help alert patients to the onset of such neurodegenerative diseases. While the impact of hormones on Alzheimer's disease remains to be clarified, altered brain hormone levels may yet provide clues in understanding how weakened neural plasticity and memory loss differ among the sexes."

While the team's study presents evidence that Alzheimer's disease mutations result in greater deterioration of brain plasticity in female mice brains compared to male mice brains, further research is required to understand the molecular basis behind this.

"Our research builds upon the work done by many labs around the world studying the molecular basis of Alzheimer's disease. Hopefully it can contribute toward solving the disease puzzle," Asst Prof Ch'ng added.

Assoc Prof Sreedharan Sajikumar said: "Studying how gender contributes to differences in disease progression will help with understanding the overall causes of Alzheimer's disease. It shows the vital importance of the need to include gender as a biological variable in all biomedical research as females and males have distinct differences in disease progression."

**Source:**

Nanyang Technological University