Poor spatial navigation could predict Alzheimer's disease years before the onset of symptoms

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People at risk of Alzheimer's disease have impaired spatial navigation prior to problems with other cognitive functions, including memory,

finds a new study led by UCL researchers.

The research, published in *Alzheimer's & Dementia*, used virtual reality to test the spatial navigation of 100 asymptomatic midlife adults, aged 43-66, from the PREVENT-Dementia prospective cohort study.

Participants had a hereditary or physiological risk of Alzheimer's disease, due to either a gene (the APOE-ε4 allele) that puts them at risk of the condition, a family history of Alzheimer's disease, or lifestyle risk factors such as low levels of physical activity. Crucially, these participants were around 25 years younger than their estimated age of dementia onset.

Led by Professor Dennis Chan, the study used a test designed by Dr. Andrea Castegnaro and Professor Neil Burgess (all from UCL Institute of Cognitive Neuroscience), in which participants were asked to navigate within a virtual environment while wearing VR headsets.

The researchers found that people at greater risk of developing Alzheimer's disease, regardless of risk factor, were selectively impaired on the VR navigation task, without a corresponding impairment on other cognitive tests. The authors say their findings suggest that impairments in spatial navigation may begin to develop years, or even decades, before the onset of any other symptoms.

First author, Dr. Coco Newton (UCL Institute of Cognitive Neuroscience), who carried out the work while at University of Cambridge, said, "Our results indicated that this type of navigation behavior change might represent the very earliest diagnostic signal in the Alzheimer's disease continuum—when people move from being unimpaired to showing manifestation of the disease."

The researchers also found that there was a strong gender difference in

how participants performed, with the impairment being observed in men and not women.

Dr. Newton added, "We are now taking these findings forward to develop a diagnostic clinical decision support tool for the NHS in the coming years, which is a completely new way of approaching diagnostics and will hopefully help people to get a more timely and accurate diagnosis.

"This is particularly important with the emergence of anti-amyloid treatments for Alzheimer's, which are considered to be most effective in the earliest stages of the disease. It also highlights the need for further study of the differing vulnerability of men and women to Alzheimer's disease and the importance of taking gender into account for both diagnosis and future treatment."

Professor Chan said, "We are excited by these findings for two main reasons. First, they improve detection of the clinical onset of Alzheimer's disease, critical for prompt application of treatments.

"Second, the VR navigation test is based on our knowledge of the spatial properties of cells in the brain's temporal lobe, and the application of cellular neuroscience to clinical populations helps bridge the gap in understanding how disease at the neuronal level can result in the clinical manifestation of disease. This knowledge gap currently represents one of the biggest barriers to progress in Alzheimer's research."

The research was carried out in collaboration with the University of Cambridge.

Dr. Richard Oakley, Associate Director of Research and Innovation at Alzheimer's Society, said, "One in three people born today will go on to develop dementia, and early and accurate diagnosis of the diseases that

cause the condition are vital for people to access the right support, plan for the future, and receive appropriate treatment. Very early symptoms of dementia can be subtle and difficult to detect, but problems with navigation are thought to be some of the first changes in Alzheimer's disease.

"This study ... used virtual reality technology showing that a healthy person's navigation abilities are linked to their dementia risk, based on genetic and environmental factors. This innovative technology is a long way from becoming a diagnostic test, but it does provide more evidence about the role of navigational abilities as an early sign of Alzheimer's disease. More work is needed to develop this technology, but it will be exciting to see how this research may offer a way to spot disease-specific changes early and help people living with dementia in future."

More information: Entorhinal-based path integration selectively predicts midlife risk of Alzheimer's disease, *Alzheimer's & Dementia* (2024). DOI: 10.1002/alz.13733

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