Biomarkers of the middle-aged brain could predict cognitive health in old age, say researchers

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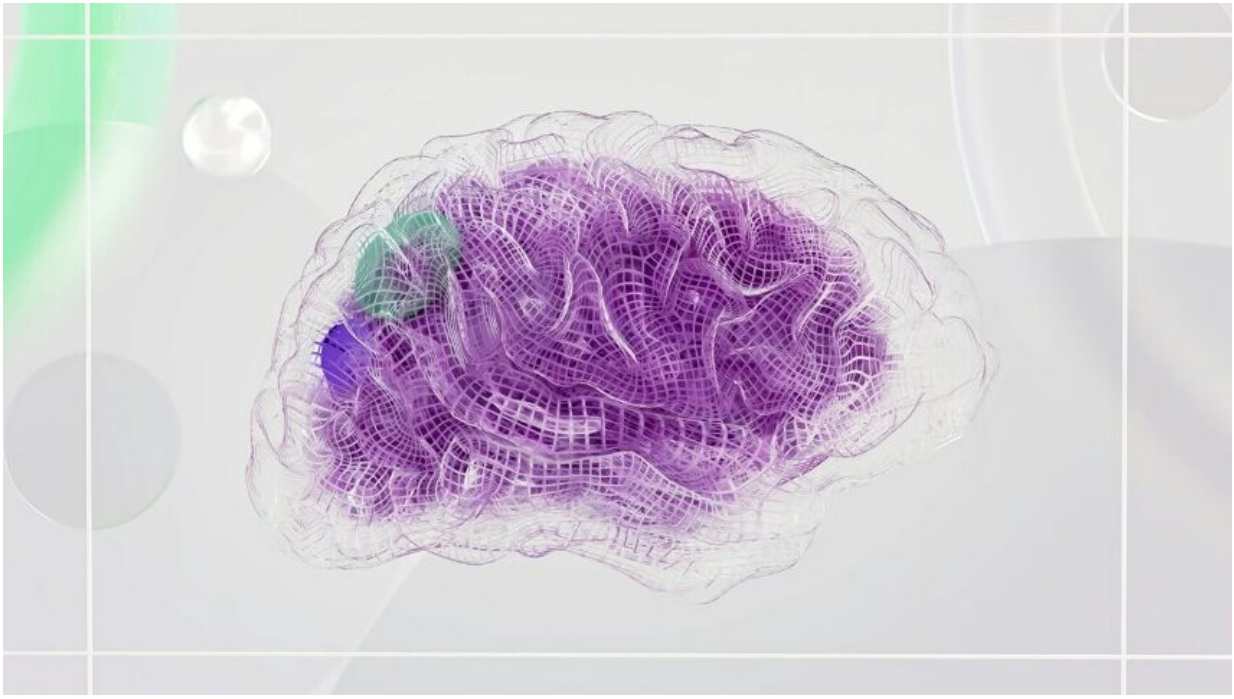

Credit: Google DeepMind from Pexels

The middle-aged brain could provide a window into future cognitive health, researchers write in a review publishing March 19 in the journal *Trends in Neurosciences*. The team reviewed evidence from human and animal studies suggesting that middle age—commonly considered as the

period between 40 and 60 or 65 years of age—marks a shift in brain aging. They argue that more research should be dedicated to middle age, a period of life that is historically understudied.

"Middle age is associated with specific and modifiable risk factors for future dementia risk," write the authors, who include neuroscientist Yvonne Nolan of APC Microbiome Ireland at University College Cork. "We encourage giving this previously understudied period of life renewed consideration."

Most studies of brain health and cognitive decline focus on older age groups, but by this time, interventions may have limited efficacy. Screening for risk of future cognitive decline could help by allowing treatment to begin earlier when it might be more effective. A better understanding of brain shifts during middle age might also help identify novel targets for therapy, the researchers say.

During middle age, the brain undergoes significant molecular, cellular, and structural changes, and many of these changes have been linked to cognitive decline, which has also been shown to accelerate during middle age.

"There is good evidence to suggest that the human brain undergoes non-linear structural and functional changes during middle age that have implications for cognitive functioning, and variation in these processes could account for individual trajectories in cognitive aging," the authors write.

Structurally, middle age is associated with changes in the volume of several brain structures, shrinking of the hippocampus (a brain structure involved in memory and learning), and decreased connectivity between different parts of the brain.

"The fourth and fifth decades of life may be a turning point in the organization of brain networks, characterized by optimal efficiency, system segregation, and modularity, followed by accelerated decay of these properties," the authors write.

Middle age is also associated with changes in gene expression, both within the brain and in other parts of the body. In the human brain, studies show increased expression of immune-related genes and decreased expression of synaptic genes. The authors also point to evidence suggesting that changes in other parts of the body may predict brain health and function.

"Factors in systemic circulation—mainly proteins secreted by various organs—are understood to mediate brain aging in terms of cognition, plasticity, adult neurogenesis, and neuroinflammation," the authors write. "Some of the largest peaks of change across the entire adult lifespan occur during middle age, as measured in plasma, peripheral blood monocytes, and muscle."

There is some evidence that exercise might aid healthy cognitive aging, but more research is needed. "Studying the intersection of aging- and exercise-related molecular processes could unveil new therapeutic targets," the authors write.

Further research is also needed to investigate observed sex differences in brain aging, as evident in the higher rate of dementia in women, the researchers say. They also note that it will be important for future studies to differentiate processes that cause declining brain health from biomarkers that reflect compensatory mechanisms.

"Ultimately, scientists will want to find novel therapeutic targets to mitigate unhealthy cognitive aging," the authors write. "We argue that applying recent trends in aging research to this period of life could

reveal novel biomarkers and possible interventions to combat cognitive decline in an increasingly older global population."

More information: The 'middle-aging' brain, *Trends in Neurosciences* (2024). DOI: 10.1016/j.tins.2024.02.001. cell.com/trends/neurosciences/… 0166-2236(24)00017-1

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