Researchers discover one cause of cognitive decline in aging population

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Researchers at Mount Sinai School of Medicine have found that certain types of specializations on nerve cells called "spines" are depleted as a person ages, causing cognitive decline in the part of the brain that mediates the highest levels of learning. These spines receive an important class of synapses that are involved with the process of learning. The discovery provides the medical community with a new therapeutic target to help prevent this loss of function. The study is published in the June 2 issue of the *Journal of Neuroscience*.

"We know that when we age, we lose certain spines, but we did not know which ones and how their loss impacted cognition," said John H. Morrison, PhD, Dean of Basic Sciences and the Graduate School of Biological Sciences and Professor of the Department of Neuroscience, Mount Sinai School of Medicine. "This study shows which spines are lost and what their impact is on brain function, giving us a foundation to research treatment interventions to protect against age-related cognitive decline."

The research team was led by Dr. Morrison and Peter R. Rapp, PhD, Adjunct Professor of Neuroscience at Mount Sinai School of Medicine, with Dani Dumitriu, MD/PhD student and Dr. Jiandong Hao, Adjunct Assistant Professor at Mount Sinai School of Medicine as the key investigators on the team and co-first authors of the paper. The team studied six young adult and nine older rhesus monkeys as they participated in a delayed response test. The monkeys watched as food was baited and hidden, and then a screen was put in front of them so

they could no longer see the location of the hidden reward.

At the beginning of the test, the screen was raised immediately and the monkeys were able to find the food reward right away. The subject's memory was tested by increasing the time that the reward was blocked from view to test if the monkeys retained where the reward was placed over longer intervals of time. Aged monkeys performed significantly worse on the tests than young monkeys, especially as the time intervals increased.

Morrison's team then used microscopic techniques to visualize the spines on nerve cells within the prefrontal cortex, an area of the brain that mediates high level learning. Nerve cells in the prefrontal cortex contain two types of spines: thin, dynamic spines, which are key to learning new things, establishing rules, and planning, and large, mushroom-shaped spines that are very stable and likely mediate long-term memories and highly stable information that we would consider expertise. The researchers determined that the older monkeys lacked the thin spines but retained the larger spines, indicating that the loss of the thin spines may be responsible for the monkeys' inability to learn and retain information during the test. For the first time, the researchers determined that the large spines were stable, which provides a synaptic basis for the observation that expertise and skills learned early in life are often maintained into old age.

"Researchers have long wondered why aging affects our ability to learn and remember new tasks and information, yet we retain well-established information, such as career expertise, well into old age," continued Dr. Morrison. "These data indicate that there is a biological reason why people cannot learn new things at an older age, but can retain knowledge learned years before, such as a professor teaching into his 80s."

Dr. Morrison noted that this study will allow for the development of

prevention strategies in youth, such as further emphasis on learning skills and broadening expertise. "The data also provide a foundation for therapies to lessen cognitive decline, through pharmaceutical and lifestyle interventions," he added.

Dr. Morrison and his team have also received funding from the National Institute on Aging (NIA) over the last ten years to study cognitive performance in monkeys undergoing menopause. The funding supports research on whether treatment with estrogen enhances cognitive performance in monkeys after menopause and which synaptic effects of estrogen are critically important for cognitive enhancement.

In future experiments, Dr. Morrison's team will test the idea of a "window of opportunity," to determine whether treatment with hormone therapy needs to be initiated soon after menopause to have the optimal cognitive impact with little risk. The National Institutes of Health (NIH)'s Women's Health Initiative showed that women who took hormone therapy were at increased risk for breast cancer and cognitive decline. However, the data only focused on women who started therapy ten years after menopause. Dr. Morrison's study will evaluate the impact of hormone therapy at the start of menopause on cognition and determine if adverse effect risk is reduced.

"We look forward to continuing to study the impact aging has on cognition and potential ways to reduce that impact," said Dr. Morrison. "While hormone therapy has been controversial in the past, we hope to show that it can provide important cognitive benefits with little risk if initiated within a certain window of opportunity."

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