Researchers show how memory is lost -- and found

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Yale University researchers can't tell you where you left your car keys- but they can tell you why you can't find them.

A new study published July 27 in the journal *Nature* shows the neural networks in the brains of the middle-aged and elderly have weaker connections and fire less robustly than in youthful ones, Intriguingly, the research suggests that this condition is reversible.

"Age-related cognitive deficits can have a serious impact on our lives in the Information Age as people often need higher cognitive functions to meet even basic needs, such as paying bills or accessing medical care," said Amy Arnsten, Professor of Neurobiology and Psychology and a member of the Kavli Institute for Neuroscience. "These abilities are critical for maintaining demanding careers and being able to live independently as we grow older."

As people age, they tend to forget things more often, are more easily distracted and disrupted by interference, and have greater difficulty with executive functions. While these age-related deficits have been known for many years, the cellular basis for these common cognitive difficulties has not been understood. The new study examined for the first time age-related changes in the activity of neurons in the prefrontal cortex (PFC), the area of the brain that is responsible for higher cognitive and executive functions.

Networks of neurons in the prefrontal cortex generate persistent firing to

keep information "in mind" even in the absence of cues from the environment. This process is called "working memory," and it allows us to recall information, such as where the car keys were left, even when that information must be constantly updated. This ability is the basis for abstract thought and reasoning, and is often called the "Mental Sketch Pad." It is also essential for executive functions, such as multi-tasking, organizing, and inhibiting inappropriate thoughts and actions.

Arnsten and her team studied the firing of prefrontal cortical neurons in young, middle-aged and aged animals as they performed a working memory task. Neurons in the prefrontal cortex of the young animals were able to maintain firing at a high rate during working memory, while neurons in older animals showed slower firing rates. However, when the researchers adjusted the neurochemical environment around the neurons to be more similar to that of a younger subject, the neuronal firing rates were restored to more youthful levels.

Arnsten said that the aging prefrontal cortex appears to accumulate excessive levels of a signaling molecule called cAMP, which can open ion channels and weaken prefrontal neuronal firing. Agents that either inhibited cAMP or blocked cAMP-sensitive ion channels were able to restore more youthful firing patterns in the aged neurons. One of the compounds that enhanced neuronal firing was guanfacine, a medication that is already approved for treating hypertension in adults, and prefrontal deficits in children, suggesting that it may be helpful in the elderly as well.

Arnsten's finding is already moving to the clinical setting. Yale is enrolling subjects in a clinical trial testing guanfacine's ability to improve working memory and executive functions in elderly subjects who do not have Alzheimer's Disease or other dementias.

Provided by Yale University