A noncoding RNA may play an important role in memory formation

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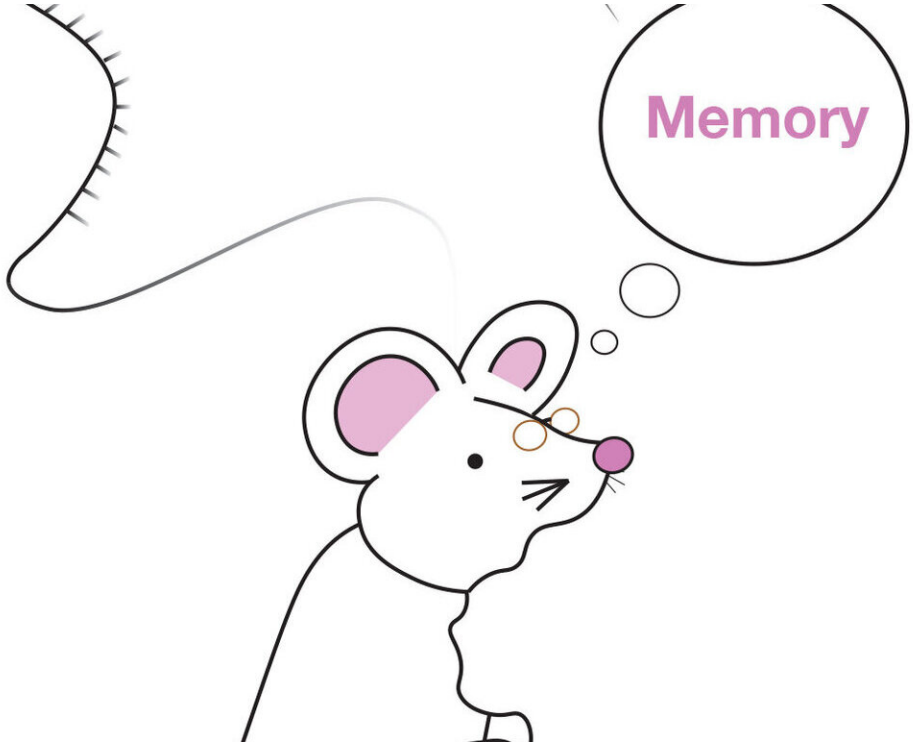

Depleting NEAT1 in old mice improved their performance in memory-associated behavior tests, whereas overexpressing NEAT1 in the hippocampus of younger mice impaired performance. Credit: Dr. Lubin

You could call this a neat discovery. Researchers at the University of Alabama at Birmingham have found that a tissue-specific, non-coding RNA called NEAT1 has a major, previously undescribed role in memory

formation. The findings are presented in a paper published in *Science Signaling* on July 2.

We have long known that DNA contains the instructions—or the code—that gives cells the genetic information they need to build and maintain an organism, much as the letters of the alphabet are the code used to make words. RNA is the messenger that transmits the code to individual cells in the form of proteins. However, there are also non-coding RNAs, which do carry instructions to a cell without coding for proteins and whose role—if any—has been poorly understood. Recently, science has come to understand that non-coding RNA may play a more important role than originally believed.

"NEAT1 is a tissue-specific, non-coding RNA found in the hippocampus region of the brain. This brain region is most associated with learning and memory," said Farah Lubin, Ph.D., associate professor in the Department of Neurobiology and primary investigator of the study. "While it has some association with cancer in other parts of the body, we have discovered that, in the hippocampus, NEAT1 appears to regulate memory formation."

Lubin says that, when NEAT1 is on, or active, we do not learn as well. But when presented with an outside learning experience, it turns off, allowing the brain to learn from the outside stimulus. She uses a car analogy. The engine might be running; but when the brakes are on, the car does not move. You have to take off the brakes and hit the gas to get the car to move.

"NEAT1 is the brake: When it is on, we aren't learning, at least not as much as we might with it off," Lubin said. "In a younger brain, when presented with stimulus that promotes learning, NEAT1 turns off. Since one of the hallmarks of aging is a decline in memory, we wondered if NEAT1 was implicated in that decline."

Lubin says one of the genes that NEAT1 acts upon is c-FOS, which is necessary for memory formation. In an aging brain, NEAT1 is on more than it is in a younger brain, interfering with the epigenetic regulation of c-FOS, which disrupts its memory functions.

Using siRNA techniques in a mouse model, Lubin's team was able to turn off NEAT1 in older mice. With NEAT1 off, the mice demonstrated normal abilities in learning and memory.

The next step was to change the level of NEAT1 in younger mice, using CRISPR/dCas9 gene-activation technology. Boosting the presence of NEAT1 in younger mice caused a decline in their ability to learn and remember.

"Turning NEAT1 off in older animals boosted memory, while increasing NEAT1 in younger animals diminished memory," Lubin said. "This gives us very strong evidence that NEAT1 and its effects on the epigenetic control of c-FOS are one of the keys to memory formation. These are significant findings, for not only did we find a novel epigenetic initiator and regulator, we identified a new role for the NEAT1 non-coding RNA. This sets the stage for more research into the potential roles played by other non-coding RNAs."

Lubin says further research should also examine the potential of using the same CRISPR/dCas9 technology to ultimately prevent NEAT1 overexpression in older humans to help boost memory formation. The goal is to find ways to enhance memory due to aging or conditions with memory deficits, such as Alzheimer's disease or other dementias.

More information: "Long noncoding RNA NEAT1 mediates neuronal histone methylation and age-related memory impairment," *Science Signaling* (2019). stke.sciencemag.org/lookup/doi …26/scisignal.aaw9277

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