July 7, 2021

In search of how memory fails

UT Alzheimer's disease study provides rare insight, thanks to rats

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Austin American-Statesman
USA Today Network

Mike Barnes remembers when his mother first started to forget.

“She would repeat herself, or she would tell stories again, or she would ask the same question again. And you could just tell that’s not the mom that I’ve always known and loved,” he said.

Barnes’ mother, Jane, now in her early 80s, first started showing signs of Alzheimer’s disease 10 years ago. Since then, Barnes has watched as her memory has slowly worsened.

Jane Barnes, with her son, Mike Barnes. Mike has watched his mother’s memory deteriorate over the 10 years. Family Photo

About five years ago, a doctor gave her a memory test and she got 20 questions right out of 30. By December of last year, she could only get three questions right. “They were simple questions,” he said. “Once you hear that and see that, you realize how bad it is.”

Alzheimer’s disease is the most common cause of dementia, a condition in which a person has difficulty with memory and other cognitive tasks. It has no cure.

But a University of Texas study published last month in Nature Communications revealed for the first time what happens when the brain makes a memory mistake. While still a long way from leading to a new treatment, the research paves the way for a deeper understanding of Alzheimer's disease that might one day benefit patients.

For the 6 million Americans living with Alzheimer's, and the half-million Texans diagnosed with the disease, a cure can't come soon enough.

Focus of the UT Alzheimer's disease study detailed

The study focused on what happens when the brain's primary memory region, the hippocampus, makes a mistake. Importantly, the hippocampus is often one of the first parts of the brain damaged by Alzheimer's disease.

The lead researcher on the project was Laura Colgin, an associate professor in the UT Department of Neuroscience. For the study, Colgin's team first took four male rats and let them scamper around a circular track marked with dots spaced evenly around the track.

Over a few weeks, they trained the rats to stop when they got to a dot marked with a piece of yellow plastic. For the final part of the training, the team removed the piece of plastic. Instead of stopping based on that visual cue, the rats had to remember where the marker was in the previous session and stop at the corresponding dot to get a treat.

Like training a dog, training a rat involves a lot of treats. "It's usually Froot Loops," Colgin said. "They're very motivated to get Froot Loops."

Next, the team put a device on the rats' heads that measured what was going on in the hippocampus as the rats ran around the track performing the memory task. Colgin's team wanted see whether the hippocampus was behaving differently during trials when the rats stopped at the wrong dot versus when they stopped at the right dot. Specifically, they measured what was going in the rats' "place cells." These remarkable cells are like a GPS system for the brain

For instance, imagine you are on a walk to get coffee from a café. As you walk past the bank, one particular place cell will activate in your hippocampus. As you walk past the bank towards a park, that first cell goes dormant and a second place cell becomes active. When you get to the café, a third place cell activates as the second one becomes quiet.

It's as if, as you walk a path in real life, a parallel path is being walked across your hippocampus, from place cell to place cell, each cell getting assigned a special place in your world. And each cell

can stay assigned to a particular place for a long time. That ability to recall some familiar place from the past has a name: memory.

By studying these place cells as the rats performed the memory task, Colgin figured out the path, or “sequence,” of cells that activated as the rats walked around the track to where they remembered they would get a Froot Loop. The study's main breakthrough was that even when the rats stopped at the wrong dot, Colgin still saw an organized sequence of place cells activating.

It "was surprising to us — that's not what we expected. We thought that the sequences would not be organized,” she said.

But while the cells still activated in an organized sequence when the rats forgot their dot, the sequence stopped too early. It’s like the “bank” place cell was activating, then the “park” place cell, but the “café” place cell never activated.

Colgin’s team also found that, when the rats failed the test, place cell activity also started later. “If you think about the different cells as runners in a relay,” said Colgin, “that first one was getting a late start out of the gate.”

Finally, Colgin found that rats seemed to “rehearse” the place cell sequences in their head while they were resting, but only when they later remembered the correct dot.

“What this study shows is so elegant,” said Michael Hausser, a neuroscientist at University College London who was not involved in the research. Taken together, these findings provide a first glimpse of what “forgetting” looks like at a cellular level, he explained.

What's the next step in the Alzheimer's research?

The next step in the research is to see whether something similar is taking place in rats with Alzheimer’s.

“We don't know, in Alzheimer's disease, what's happening,” Colgin said. “Are the memories not getting stored, is that the problem? Or are the memories getting stored, but there's a problem in the machinery to retrieve the memories? That kind of information we can figure out from doing this kind of study in a rat model of Alzheimer's disease.”

If faulty place cell sequences are indeed leading to problems with memory in these rats with dementia, Colgin’s research could lead to new options for fixing the problems.

“If you know what the correct sequence is, and it seems like the network is heading towards an incorrect sequence, maybe you could correct it on the fly and thereby improve the recall of the memory,” Hausser said. “That’s science fiction. But in principle we have the tools already.”

Alzheimer’s is the sixth-leading cause of death in the United States and dementia-related deaths have spiked 26% in Texas since the start of the pandemic, according to the Alzheimer’s Association.

Last month, the federal Food and Drug Administration approved a controversial new drug known by the brand name Aduhelm to treat Alzheimer’s disease. Although scientists are divided on the effectiveness of the drug, which targets toxic clumps in the brain called beta-amyloid, it will be the first new treatment option for people living with Alzheimer’s disease in more than two decades.

Andrea Taurins, executive director of the Capital of Texas chapter of the Alzheimer’s Association, a nonprofit advocacy group, said she’s optimistic that basic research like Colgin’s study might one day help turn the tide of the disease.

“The more we can understand the causes of some of these symptoms,” she said, “the better we are at understanding how we can get closer to a cure.”

IF YOU NEED HELP

If you are struggling with the effects of Alzheimer’s disease, you can reach out to the Alzheimer’s Association’s 24-hour hotline at 800-272-3900 or go online at alz.org/texascapital.