What are memories made of? New study sheds light on key protein

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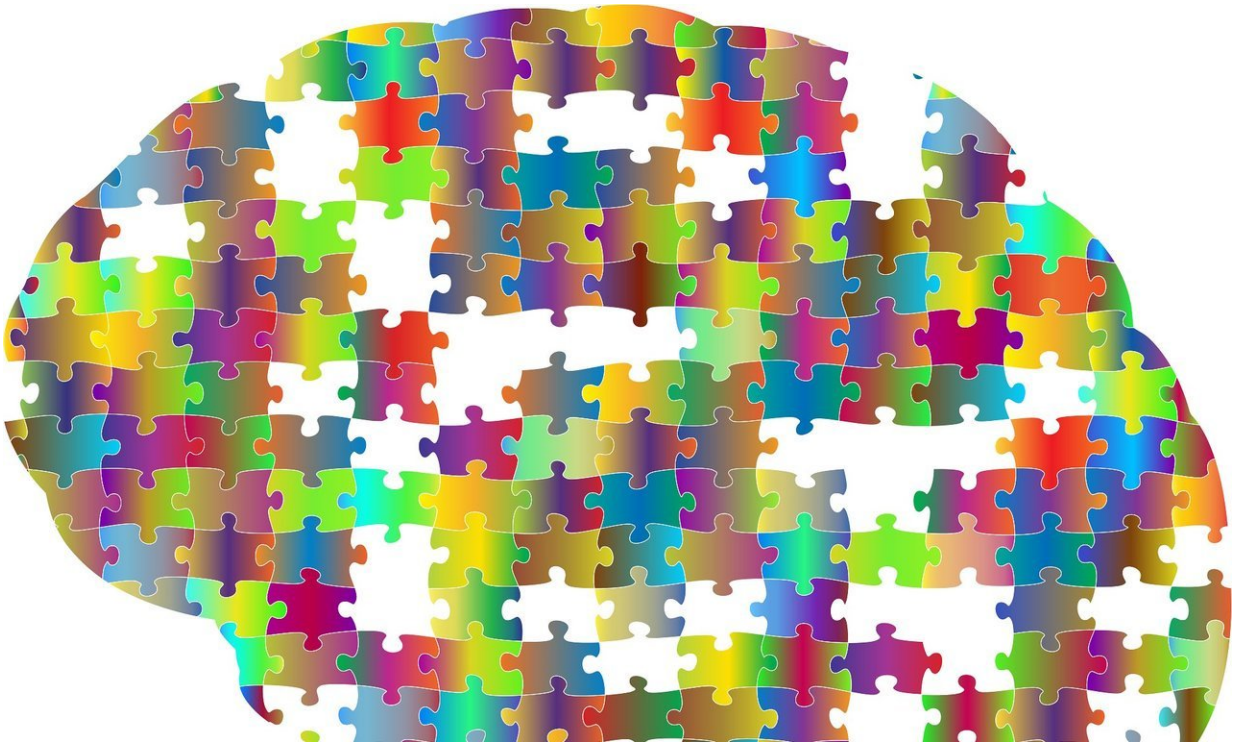

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Ask a nonscientist what memories are made of and you'll likely conjure images of childhood birthday parties or wedding days. Charles Hoeffer thinks about proteins.

For five years, the assistant professor of integrative physiology at CU

Boulder has been working to better understand a protein called AKT, which is ubiquitous in brain tissue and instrumental in enabling the brain to adapt to new experiences and lay down new memories.

Until now, scientists have known very little about what it does in the brain.

But in a new paper funded by the National Institutes of Health, Hoeffer and his co-authors spell it out for the first time, showing that AKT comes in three distinct varieties residing in different kinds of brain cells and affecting brain health in very distinct ways.

The discovery could lead to new, more targeted treatments for everything from glioblastoma—the brain cancer Sen. John McCain has—to Alzheimer's disease and schizophrenia.

"AKT is a central protein that has been implicated in a bevy of neurological diseases yet we know amazingly little about it," Hoeffer said. "Our paper is the first to comprehensively examine what its different forms are doing in the brain and where."

Discovered in the 1970s and known best as an "oncogene" (one that, when mutated, can promote cancer), AKT has more recently been identified as a key player in promoting "synaptic plasticity," the brain's ability to strengthen cellular connections in response to experience.

"Let's say you see a great white shark and you are scared and your brain wants to form a memory of what's going on. You have to make new proteins to encode that memory," he said. AKT is one of the first proteins to come online, a central switch that turns on the memory factory.

But not all AKTs are created equal.

For the study, Hoeffer's team silenced the three different isoforms, or varieties, of AKT in mice and observed their brain activity.

They made a number of key discoveries:

AKT2 is found exclusively in astroglia, the supportive, star-shaped cells in the brain and spinal cord that are often impacted in brain cancer and brain injury.

"That is a really important finding," said co-author Josien Levenga, who worked on the project as a postdoctoral researcher at CU Boulder. "If you could develop a drug that targeted only AKT2 without impacting other forms, it might be more effective in treating certain issues with fewer side-effects."

The researchers also found that AKT1 is ubiquitous in neurons and appears to be the most important form in promoting the strengthening of synapses in response to experience, aka memory formation. (This finding is in line with previous research showing that mutations in AKT1 boost risk of schizophrenia and other brain disorders associated with a flaw in the way a patient perceives or remembers experiences.)

AKT3 appears to play a key role in brain growth, with mice whose AKT3 gene is silenced showing smaller brain size.

"Before this, there was an assumption that they all did basically the same thing in the same cells in the same way. Now we know better," Hoeffer said.

He notes that pan-AKT inhibitors have already been developed for cancer treatment, but he envisions a day when drugs could be developed to target more specific versions of the protein (AKT1 enhancers for Alzheimer's and schizophrenia, AKT2 inhibitors for cancer), leaving the

others forms untouched, preventing side-effects.

More animal research is underway to determine what happens to behavior when different forms of the protein go awry.

"Isoform specific treatments hold great promise for the design of targeted therapies to treat neurological diseases with much greater efficacy and accuracy than those utilizing a one-size-fits-all approach," the authors conclude. "This study is an important step in that direction."

The study is published in *eLife*.

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