

# How old memories fade away: Discovery of a gene essential for memory extinction could lead to new PTSD treatments

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Credit: Christine Daniloff

If you got beat up by a bully on your walk home from school every day, you would probably become very afraid of the spot where you usually met him. However, if the bully moved out of town, you would gradually cease to fear that area.

Neuroscientists call this phenomenon "memory extinction": Conditioned responses fade away as older memories are replaced with [new](#)

[experiences.](#)

A new study from MIT reveals a gene that is critical to the process of memory extinction. Enhancing the activity of this gene, known as Tet1, might benefit people with posttraumatic stress disorder (PTSD) by making it easier to replace fearful memories with more positive associations, says Li-Huei Tsai, director of MIT's Picower Institute for Learning and Memory.

The Tet1 gene appears to control a small group of other [genes](#) necessary for memory extinction. "If there is a way to significantly boost the expression of these genes, then extinction learning is going to be much more active," says Tsai, the Picower Professor of Neuroscience at MIT and senior author of a paper appearing in the Sept. 18 issue of the journal *Neuron*.

The paper's lead authors are Andrii Rudenko, a postdoc at the Picower Institute, and Meelad Dawlaty, a postdoc at the Whitehead Institute.

## **New and old memories**

Tsai's team worked with researchers in Rudolf Jaenisch's lab at the Whitehead to study mice with the Tet1 gene knocked out. Tet1 and other Tet proteins help regulate the modifications of DNA that determine whether a particular gene will be expressed or not. Tet proteins are very abundant in the brain, which made scientists suspect they might be involved in learning and memory.

To their surprise, the researchers found that mice without Tet1 were perfectly able to form memories and learn new tasks. However, when the team began to study memory extinction, significant differences emerged.

To measure the mice's ability to extinguish memories, the researchers conditioned the mice to fear a particular cage where they received a mild shock. Once the memory was formed, the researchers then put the mice in the cage but did not deliver the shock. After a while, mice with normal Tet1 levels lost their fear of the cage as new memories replaced the old ones.

"What happens during memory extinction is not erasure of the original memory," Tsai says. "The old trace of memory is telling the mice that this place is dangerous. But the new memory informs the mice that this place is actually safe. There are two choices of memory that are competing with each other."

In normal mice, the new memory wins out. However, mice lacking Tet1 remain fearful. "They don't relearn properly," Rudenko says. "They're kind of getting stuck and cannot extinguish the old memory."

In another set of experiments involving spatial memory, the researchers found that mice lacking the Tet1 gene were able to learn to navigate a water maze, but were unable to extinguish the memory.

## **Control of memory genes**

The researchers found that Tet1 exerts its effects on memory by altering the levels of DNA methylation, a modification that controls access to genes. High methylation levels block the promoter regions of genes and prevent them from being turned on, while lower levels allow them to be expressed.

Many proteins that methylate DNA have been identified, but Tet1 and other Tet proteins have the reverse effect, removing DNA methylation. The MIT team found that mice lacking Tet1 had much lower levels of hydroxymethylation—an intermediate step in the removal of

methylation—in the hippocampus and the cortex, which are both key to [learning and memory](#).

These changes in demethylation were most dramatic in a group of about 200 genes, including a small subset of so-called "immediate early genes," which are critical for [memory formation](#). In mice without Tet1, the immediate early genes were very highly methylated, making it difficult for those genes to be turned on.

In the promoter region of an immediate early gene known as Npas4—which Yingxi Li, the Frederick A. and Carole J. Middleton Career Development Assistant Professor of Neuroscience at MIT, recently showed regulates other immediate early genes—the researchers found methylation levels close to 60 percent, compared to 8 percent in normal mice.

"It's a huge increase in methylation, and we think that is most likely to explain why Npas4 is so drastically downregulated in the Tet1 knockout mice," Tsai says.

## **Keeping genes poised**

The researchers also discovered why the Tet1-deficient mice are still able to learn new things. During fear conditioning, methylation of the Npas4 gene goes down to around 20 percent, which appears to be low enough for the expression of Npas4 to turn on and help create new memories. The researchers suspect the fear stimulus is so strong that it activates other demethylation proteins—possibly Tet2 or Tet3—that can compensate for the lack of Tet1.

During the memory-extinction training, however, the mice do not experience such a strong stimulus, so methylation levels remain high (around 40 percent) and Npas4 does not turn on.

The findings suggest that a threshold level of methylation is necessary for gene expression to take place, and that the job of Tet1 is to maintain low methylation, ensuring that the genes necessary for memory formation are poised and ready to turn on at the moment they are needed.

The researchers are now looking for ways to increase Tet1 levels artificially and studying whether such a boost could enhance memory extinction. They are also studying the effects of eliminating two or all three of the Tet enzymes.

"This will not only help us further delineate epigenetic regulation of memory formation and extinction, but will also unravel other potential functions of Tets and methylation in the brain beyond memory [extinction](#)," Dawlaty says.

**More information:** [www.sciencedirect.com/science/ ...  
ii/S0896627313007149](http://www.sciencedirect.com/science/.../S0896627313007149)

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