Study identifies drug that could improve treatment of posttraumatic stress disorder

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Credit: CHRISTINE DANILOFF/MIT

Nearly 8 million Americans suffer from posttraumatic stress disorder (PTSD), a condition marked by severe anxiety stemming from a traumatic event such as a battle or violent attack.

Many patients undergo psychotherapy designed to help them re-experience their traumatic memory in a safe environment so as to help them make sense of the events and overcome their fear. However, such memories can be so entrenched that this therapy doesn't always work,

especially when the traumatic event occurred many years earlier.

MIT neuroscientists have now shown that they can extinguish well-established traumatic memories in mice by giving them a type of drug called an HDAC2 inhibitor, which makes the brain's memories more malleable, under the right conditions. Giving this type of drug to human patients receiving psychotherapy may be much more effective than psychotherapy alone, says Li-Huei Tsai, director of MIT's Picower Institute for Learning and Memory.

"By inhibiting HDAC2 activity, we can drive dramatic structural changes in the brain. What happens is the brain becomes more plastic, more capable of forming very strong new memories that will override the old fearful memories," says Tsai, the senior author of a paper describing the findings in the Jan. 16 issue of *Cell*.

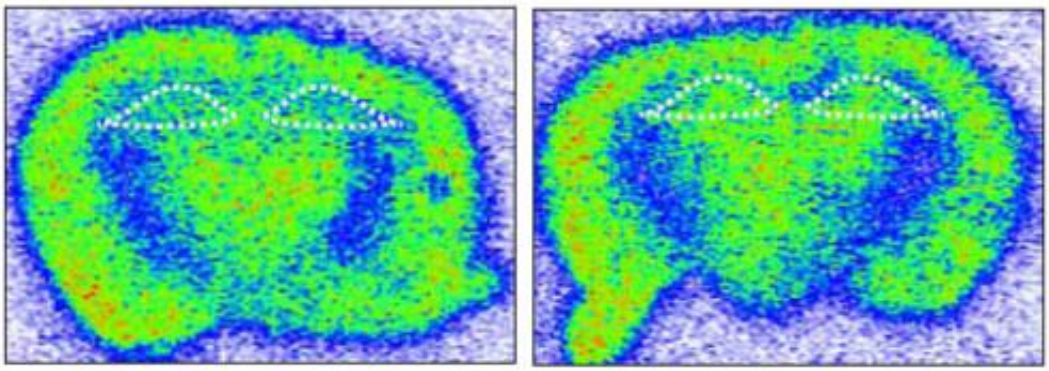
The new study also reveals the molecular mechanism explaining why older memories are harder to extinguish. Lead authors of the paper are former Picower Institute postdoc Johannes Graff and Nadine Joseph, a technical assistant at the Picower Institute.

Genes and memories

Tsai's lab has previously shown that when memories are formed, neurons' chromatin—DNA packaged with proteins—undergoes extensive remodeling. These chromatin modifications make it easier to activate the genes necessary to create new memories.

In this study, the researchers focused on chromatin modifications that occur when previously acquired memories are extinguished. To do this, they first trained mice to fear a particular chamber—by administering a mild foot shock—and then tried to recondition the mice so they no longer feared it, which was done by placing the mice in the chamber

where they received the shock, without delivering the shock again.



Metabolic activity (green and red colors) in the hippocampus (white dotted line) of animals that underwent extinction training in combination with HDACis (right) is significantly higher than in animals that underwent extinction training alone (left). Metabolic activity serves to estimate the learning capacity of an animal. Credit: *Cell*, Gräff et al.

This training proved successful in mice that had experienced the traumatic event only 24 hours before the reconditioning. However, in mice whose memories were 30 days old, it was impossible to eliminate the fearful memory.

The researchers also found that in the brains of mice with 24-hour-old memories, extensive chromatin remodeling occurred during the reconditioning. For several hours after the mice were placed back in the feared chamber, there was a dramatic increase in histone acetylation of memory-related genes, caused by inactivation of the protein HDAC2. That histone acetylation makes genes more accessible, turning on the processes needed to form new memories or overwrite old ones.

In mice with 30-day-old memories, however, there was no change in

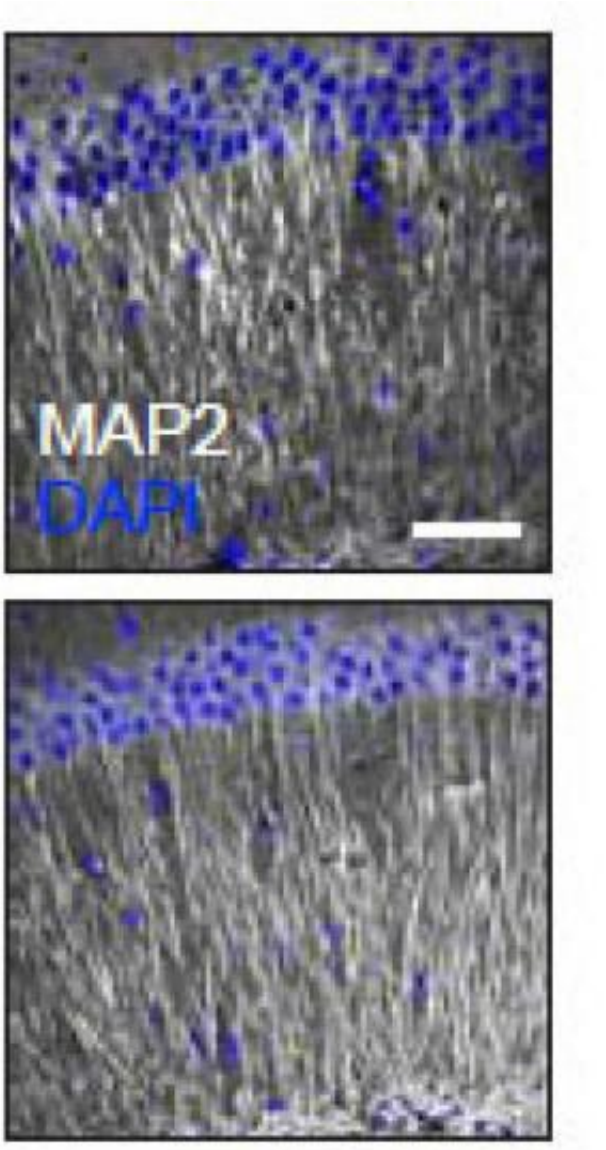
histone acetylation. This suggests that re-exposure to a fearful memory opens a window of opportunity during which the memory can be altered, but only if the memory has recently been formed, Tsai says.

"If you do something within this window of time, then you have the possibility of modifying the memory or forming a new trace of memory that actually instructs the animal that this is not such a dangerous place," she says. "However, the older the memory is, the harder it is to really change that memory."

Based on this finding, the researchers decided to treat mice with 30-day-old memories with an HDAC2 inhibitor shortly after re-exposure to the feared chamber. Following this treatment, the traumatic memories were extinguished just as easily as in the mice with 24-hour-old memories.

The researchers also found that HDAC2 inhibitor treatment turns on a group of key genes known as immediate early genes, which then activate other genes necessary for memory formation. They also saw an increase in the number of connections among neurons in the hippocampus, where memories are formed, and in the strength of communication among these neurons.

"Our experiments really strongly argue that either the old memories are permanently being modified, or a new much more potent memory is formed that completely overwrites the old memory," Tsai says.



The abundance of dendrite in the hippocampus of animals that underwent extinction training in combination of HDACis (lower) is significantly higher than in animals s that underwent extinction training alone (upper). Credit: *Cell*, Gräff et al.

Treating anxiety

Some HDAC2 inhibitors have been approved to treat cancer, and Tsai

says she believes it is worth trying such drugs to treat PTSD. "I hope this will convince people to seriously think about taking this into clinical trials and seeing how well it works," she says.

Such drugs might also be useful in treating people who suffer from phobias and other anxiety disorders, she adds.

Tsai's lab is now studying what happens to memory traces when re-exposure to traumatic memories occurs at different times. It is already known that memories are formed in the hippocampus and then transferred to the cortex for longer-term storage. It appears that the HDAC2 inhibitor treatment may somehow restore the memory to the hippocampus so it can be extinguished, Tsai says.

More information: *Cell*, Gräff et al.: "Epigenetic priming of memory updating during reconsolidation to attenuate remote fear memories." dx.doi.org/10.1016/j.cell.2013.12.020

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