**BRIEF ACCESSIBLE REVIEW**

# Reminiscence of Good Old Times

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Joe is depressed. He lost his job and has no motivation to look for the next one. He can't find any pleasure in things; he doesn't even care for his favorite burger anymore. He has given up. Jane is struggling to understand what has happened to him. She tells him to try to think about all the good times they have had. *"Let's go out with friends, have some fun, you'll snap out of it in no time!"* Can he?

If you make a leap of faith and presume that mice may have similar problems, then a recent research article (1) in the journal *Nature* by Tonegawa's group from the Picower Institute offers interesting insights. This study, led by Steve Ramirez and Xu Liu, takes advantage of the coolest trick up neuroscientists' sleeves: **optogenetics**. This relatively new technique enables scientists to activate or silence genetically modified brain cells in mice by shining a laser on them through tiny holes in the skull, while the animals are alive and freely behaving. The real trick is in the "genetics" part of the technique: the scientists *tag* a specific set of brain cells that will become responsive to the laser, by inserting genes that instruct the brain cells to make light-sensitive channel proteins. Since the laser does not affect normal cells, it is possible to perturb very specific subsets of brain cells and study their function.

When mice are chronically stressed, e.g. by being confined to a small plastic tube for a few hours every day, they display behaviors that are not unlike what Joe is doing. Suspend the mice in the air by their tails, they give up quicker. Give them a choice of regular water versus sugar water; they don't care.

These are the types of experiments used to test antidepressant medications in mice. If a potential medicine helps the stressed mice keep struggling longer when suspended, or prefer the sugar water as they normally would, then the medicine may also help Joe with his lack of motivation and pleasure.

Ramirez and colleagues asked a question similar to Jane's. **What if we could activate the memories of the good old times at will?** Would that cure mouse depression? We do not know how memories are stored down to the last detail, but Dr. Tonegawa's group has a close approximation: a **memory engram,** a specific set of brain cells that are all activated together during a particular experience. Using a clever genetic technique, they were able to tag memory engrams (cells in a part of the brain called the hippocampus, which is critical for memory formation) with the aforementioned light-sensitive proteins, so they can activate the same memory at will (Figure 1A). As a positive experience, some male mice had private time with a female (*good old times!*) while others had quiet time by themselves (a neutral experience). Then, both groups were chronically stressed. As expected, these mice displayed depression-like behaviors (Figure 1B). When the neuroscientists turned on the lasers and activated the previously tagged brain cells, they observed a difference between the groups. Activating the neutral experience engram had no

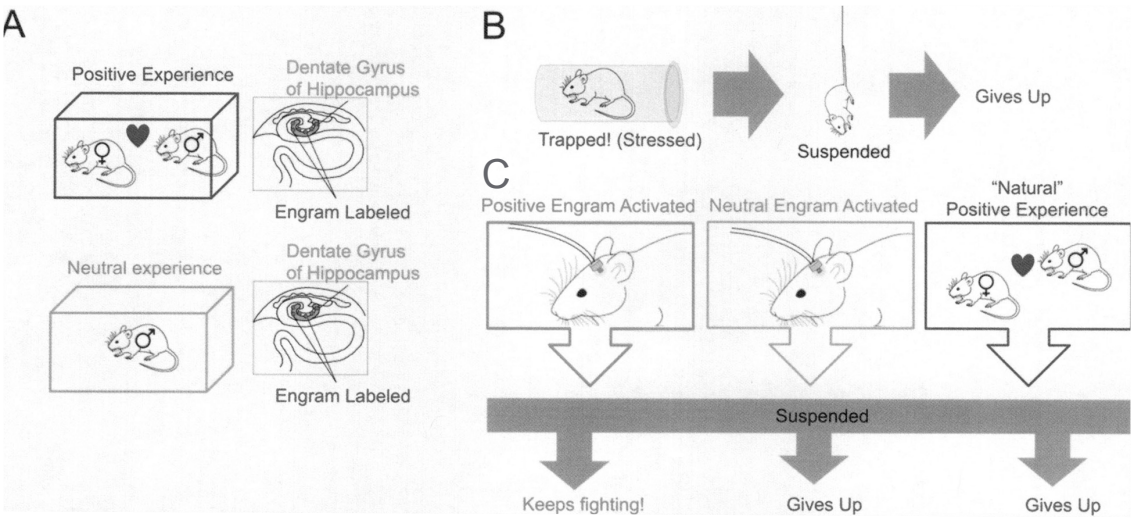


**Figure 1. Activating positive memory engrams rescues depression-related behavior.**

(1A) In this study, scientists used light sensitive proteins to label memory engrams in mice during either a positive or neutral experience. (1B) Mice were then exposed to a stressful situation (chronic immobilization stress) and assessed by the tail suspension test (TST) as a measure of passive escape (or depression-like) behaviors. (1C) Optically reactivating the cells that were active during a positive experience, but not a neutral experience increased the time the mice struggled, suggesting some rescue of depression-like behaviors. Re-exposing the mouse to the positive reward did not increase the time the mice struggled on the TST. (Figure art by Bercin K. Cenik.)

effect, but activating the positive experience engram diminished the depression-like behaviors (Figure 1C). Interestingly, a single activation of the engram had fleeting effects: when the mice were tested 5 days later, they were still acting as if depressed. However, when the positive engram was activated daily for 5 days, the antidepressant effect seemed to last at least 24 hours. Further experiments showed that other brain areas connected "downstream" to the memory area were also activated once the memory engram was triggered.

So is Jane right? Could Joe reminisce about the good old times and snap out of his depression? A simple control experiment in Ramirez's study may be pertinent. What if you simply place the depressed male mouse back with the female? You might expect this would also activate the memories. Interestingly, Ramirez and colleagues found this "natural reward" condition did not have a significant effect on depression-like behaviors. They speculate that, unlike the artificial triggering of the memory engram, natural exposure to the reward may not be effective in activating other "downstream" brain areas. It is tempting to conjecture that once a mouse is depressed, the positive memories are as though locked away, inaccessible by any means short of inserting a fiber optic cable down to the memory center. Perhaps this is why Joe cannot envision the prospect of relief yet. Fortunately there are effective treatments for his condition: antidepressant medication and psychotherapy. Yet these take weeks, if not months, to work. Wouldn't it be great to flip on a light switch and go back to the good old times, like Ramirez's mice?

## AUTHOR CONTRIBUTIONS

Basar Cenik, MD, PhD is a PGY3 resident from the University of Texas Southwestern Medical Center and a 2015-16 NNCI Scholar. The National Neuroscience Curriculum Initiative is a collaborative effort with AADPRT and the American Psychiatric Association (APA) Council on Medical Education and Lifelong Learning and receives support from the NIH (R25 MH10107602S1) 

## FOOTNOTES

1) Ramirez, S., Liu, X., MacDonald, C.J., Moffa, A., Zhou, J., Redondo, R.L., and Tonegawa, S. 2015. Activating positive memory engrams suppresses depression-like behaviour. Nature 522, 335-339.