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Transplanted interneurons can help reduce fear in mice

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The expression "once bitten, twice shy" is an illustration of how a bad experience can induce fear and caution. How to effectively reduce the memory of aversive events is a fundamental question in neuroscience. Scientists in China are reporting that by transplanting mouse embryonic interneurons into the brains of mice and combining that procedure with training to lessen fear, they can help to reduce the fear response. The study is being published December 8 in *Neuron*.

"Anxiety and fear-related disorders such as post-traumatic stress disorder [PTSD] cause great suffering and impose high costs to society," says Yong-Chun Yu, a professor at the Institutes of Brain Science at Fudan University in Shanghai and the study's senior author. "Pharmacological and behavioral treatments of PTSD can reduce symptoms, but many people tend to relapse. There's a pressing need for new strategies to treat these refractory cases."

In the study, the researchers used traditional conditioning to instill fear in the mice. They exposed them to a sound as a neutral stimulus, followed by a mild shock to the foot. To determine the level of fear, they measured the amount of time the mice exhibited freezing behavior--the natural sympathetic fear response in prey animals that is indicated by crouching. They then conducted fear extinction training, in which the mice were exposed to the sound but not the shock. After a few rounds, the freezing response times were significantly reduced.

To determine the contribution that transplanting immature interneurons into the amygdala--a brain structure known to be involved in processing of fear and other emotions--could have on fear extinction training, they inserted medial ganglionic eminence (MGE) cells taken from embryos into the amygdala regions of mature mice. The transplanted cells were labeled with

embryos into the amygdala regions of mature mice. The transplanted cells were labeled with green fluorescent protein, enabling the researchers to experimentally confirm that the new cells were integrating into the brains' circuits.

"We found that although the transplanted interneurons did not alter the formation of fear memories, they reduced recovery and renewal of fear after extinction training," Yu says. However, transplantation of the neurons alone was not enough to reduce fear memories, indicating that the MGE cells were boosting the effectiveness of that training.

"Unexpectedly, we observed that the erasure of fear memory is facilitated only by transplanted immature interneurons--two weeks after transplantation," he adds. "Previous studies had indicated that transplanted MGE cells induce plasticity when they are relatively mature--four weeks after transplantation."

Further studies indicated that the transplanted immature interneurons reactivated a juvenile-like plasticity in the mature amygdala. "Likely related to the changes in the expression of perineuronal nets (PNNs), which are responsible for synaptic stabilization, we found that transplanted immature neurons enhance synaptic plasticity in the amygdala's circuits by disrupting PNNs, converting the amygdala to a juvenile stage," Yu says.

Additional experiments are required to determine how these transplanted immature interneurons rejuvenate the mature circuits. "We still don't know the mechanism by which these immature neurons modulate the fear extinction behavior in the mice," he concludes. "We also need to determine the exact subtype of transplanted interneurons and the exact subregion in the amygdala that are responsible for these behavioral effects."

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Neuron, Yang et al: "Fear Erasure Facilitated by Immature Inhibitory Neuron Transplantation." http://www.cell.com/neuron/fulltext/S0896-6273(16)30856-X