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Brain scientists extend map of fear memory formation

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Draw a map of the brain when fear and anxiety are involved, and the amygdala -- the brain's almond-shaped center for panic and fight-or-flight responses -- looms large.

But the amygdala doesn't do its job alone. Scientists at Emory University have recently built upon work from others, extending the fear map to part of the brain known as the prelimbic cortex.

Researchers led by Kerry Ressler, MD, PhD, found that mice lacking a critical growth factor in the prelimbic cortex have trouble remembering to fear electric shocks. The discovery could help improve diagnosis and treatment for anxiety disorders such as post-traumatic stress disorder and phobias.

The results are published online this week in the Proceedings of the National Academy of Sciences. Ressler is a researcher at Emory University's Yerkes National Primate Research Center, an associate professor of psychiatry and behavioral sciences at Emory University School of Medicine and a member of the Atlanta-based Center for Behavioral Neuroscience. He is the first practicing psychiatrist to be appointed a Howard Hughes Medical Investigator. The research was conducted in mice at the Yerkes Research Center.

Scientists describe the molecule BDNF (brain-derived neurotrophic factor) as Miracle-Gro for brain cells. It's a protein that pushes brain cells to withstand stress and make new connections. In other parts of the brain such as the amygdala, interfering with BDNF's effects blocks the acquisition of fear memory.

Some variations in the human gene for BDNF are thought to increase the risk for anxiety disorders and even change the anatomy of the prefrontal cortex in affected individuals.

"The prelimbic cortex is part of the medial prefrontal cortex, which appears to be important for emotional regulation in rodents as well as humans," Ressler says. "Evidence is building that these regions may be dysregulated or even over-active in fear and anxiety disorders in humans.

Working with Ressler, postdoctoral associate Dennis Choi and colleagues took advantage of a strain of genetically engineered mice that lack the BDNF gene in certain parts of the brain. These include the prelimbic cortex but exclude the amygdala and other regions such as the hippocampus.

If mice are electrically shocked just after they hear a certain tone, they gradually learn to fear that tone, and they show that fear by freezing. The BDNF-altered mice could run around and respond to shocks just as well, and could still learn to fear tones "in the moment."

However, they seemed to have trouble retaining fear memories as time passed. After learning to fear the tone, the altered mice didn't freeze as much, compared to normal mice, one hour or a day later. Using a different approach, the researchers also found that mice injected with a virus that eliminates the BDNF gene in the prelimbic cortex display similar characteristics.

"This work is important for extending our understanding of how BDNF is important for neuronal plasticity, learning and memory," Ressler says. "Together with our previous work, these data suggest that preventing neural plasticity in very precise, but critical brain regions, can have vastly different effects on emotional memory.

"It is becoming increasingly clear that these prefrontal cortex regions are functionally associated with regions of the brain known for a long time to be involved in emotion, such as the amygdala and hippocampus," he adds. "Understanding the molecular and cellular mechanisms of these connections in rodent models will provide scientists a better understanding of how these similar areas are functioning in humans."

A related paper in *PNAS* from Keqiang Ye, PhD, associate professor of pathology and laboratory medicine at Emory, and colleagues describes a family of compounds that can mimic BDNF.

Provided by Emory University

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