Study finds 'frozen' fear response may underlie PTSD

December 4 2019, by Bill Snyder

Credit: George Hodan/public domain

Learned fear responses enable animals—including humans—to flee or freeze in the face of a perceived threat. But if these behaviors persist after the danger lifts, they can become paralyzing and disabling. That's a key element of posttraumatic stress disorder (PTSD).

To explore how fear becomes entrenched, researchers at Vanderbilt

University Medical Center have traveled down the precise neuronal pathways in the brains of mice that trigger fear responses, and which normally extinguish the behaviors once the danger has passed.

This scientific journey, detailed recently in *Nature Neuroscience*, challenges conventional wisdom about how the brain is "remodeled" in response to the intrusion—and subsequent removal—of fear-inducing stimuli.

It's widely assumed that the brain's advanced seat of cognition, the cerebral cortex, decides how to respond to a threat and its order "filters down" to a more primitive part of the brain, the central amygdala, where the flee-or-freeze response is executed and terminated.

But the Vanderbilt scientists found something unexpected: initiation and termination of learned freezing responses occur in cortical parts of the amygdala via a flexible remodeling of excitation onto two distinct subtypes of central amygdala "output channels."

It is here that the animal learns to fear certain stimuli through one neuronal channel and "unlearns" the fear through the other channel once the threat is gone.

"You don't want too much thinking going on" in the face of danger, explained Sachin Patel, MD, Ph.D., the paper's corresponding author and director of the Division of General Psychiatry at Vanderbilt.

"You want very distinct outputs to happen independently so the animal can choose very quickly—should I freeze, run or just go about my business? That's part of the novelty here.

"There's a lot of learning-related plasticity and remodeling in the brain that's occurring at some of these more 'primitive' central amygdala

synapses rather than just within the cortical-like areas," he said.

How might this knowledge apply to the human condition?

People who have been exposed to stress or trauma can form associations between environmental cues and the fear that their lives are in danger. If the association persists after the threat is gone and the environmental cues continue to trigger anxiety and fear, that can lead to PTSD.

"It's like they're stuck on the freezing channel and can't flip back to the … normal behavior channel," said Patel, also the James G. Blakemore Professor of Psychiatry and professor of Molecular Physiology and Biophysics and Pharmacology. "That's a theory (but) it might be related to some sort of deficit in this synaptic flexibility mechanism we've discovered."

Currently PTSD is treated by gradually exposing patients to the environmental cues that trigger their fear responses to help their brains "re-learn" to extinguish the behaviors. But exposure therapy is intense. Some patients can't tolerate the anxiety it can cause.

The next step for the researchers is to look for receptors or proteins expressed by cells in one channel but not in the other. "That would provide opportunities to pharmacologically manipulate the dynamic switching between those channels," Patel said.

"It's not so far-fetched and people are doing it" he added. "If we knew that they had a different molecular composition, maybe there's a way that we could inhibit the 'freezing' channel, the fear channel, and promote the other channel."

Patel said the knowledge gained about the fear response may advance understanding of other brain disorders including drug and alcohol abuse.

"Addiction in part is driven by aberrant learning … cues triggering drug seeking and relapse," he said. "We know the amygdala is important in both fear-learning as well as making associations between rewarding effects of drugs and environmental cues. A lot of the same mechanisms might be at play."

More information: Nolan D. Hartley et al. Dynamic remodeling of a basolateral-to-central amygdala glutamatergic circuit across fear states, *Nature Neuroscience* (2019). DOI: 10.1038/s41593-019-0528-7

Provided by Vanderbilt University

Citation: Study finds 'frozen' fear response may underlie PTSD (2019, December 4) retrieved 9 April 2024 from https://medicalxpress.com/news/2019-12-frozen-response-underlie-ptsd.html

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