Researchers' preclinical trial upends conventional wisdom about responses to fear

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Northeastern assistant professor of psychology Rebecca Shansky provides insights into new treatments for post-traumatic stress disorder with a preclinical study that distinguishes how males and females respond to traumatic events. Credit: Adam Glanzman/Northeastern University

Fear. You've been there: Your heart races, even jumps to your throat.

Your hands grow clammy and your stomach churns. Your mind goes blank.

Rats have been there, too. We don't know their feelings, of course, but we do know their response: They freeze in their tracks. Or at least that's been the consensus among scientists since 1899, when experimental psychologist Willard Stanton Small first noted the behavior.

But now new research led by Rebecca Shansky, assistant professor of psychology at Northeastern University, upends that conventional wisdom.

In a study recently published in the online journal *eLife*, Shansky's team found that female rats often respond to fear by "darting." "They start running around like crazy," Shansky says. "It looks like they're trying to escape."

In addition, the darting rats were more successful at integrating a process that suppressed the fear response, says Shansky, exhibiting a "cognitive flexibility" that the freezers lacked.

The findings not only raise questions about the veracity of previous studies that rely on freezing to indicate fear. They could also lead to better treatments for post-traumatic stress disorder, a condition that, in the U.S. alone, affects about 8 mil-lion adults during a given year, according to the National Center for PTSD of the U.S. Department of Veterans Affairs.

"If we can harness whatever is going on when an animal becomes a darter," says Shansky, "we could try to apply that to treatments."

Shansky had not set out to challenge a century-old assumption. Rather, she stumbled across the findings while performing a common behavioral

test called "fear conditioning" in an effort to see how individual males and females differed in their fear responses, and to explore what brain changes related to those differences.

The test involved teaching the animals to associate a tone with a foot shock, and then—with a video camera connected to a computer—measuring the duration of their reaction as the training proceeded. "Animals who exhibit low levels of freezing would traditionally be interpreted as either not learning or naturally fear-less," says Shansky.

Because computers may mistake sleeping for freezing, graduate student Tina Gruene, PhD'19, watched the videos afterward as a backup check. What she saw shocked her: Scores of the female rats not only didn't freeze at the sound of the tone; they darted hither and yon, as if looking for an exit.

What did that mean? The study had a large number of rats—120 as opposed to the standard 20—so Shansky set out to quantify the behavior. "We wanted to see if this was something real," she says.

The researchers fed the videos into a behavioral analysis program that tracks motion to monitor the velocity of the animals' movement. Their plotted graphs confirmed their hunch: Darting was not a sign of fearlessness or an inability to learn. It was just as much a learned response as freezing.

"The learning curve for darting was the same as the learning curve for freezing," says Shansky, pointing to graphics in the paper. "But we saw it almost exclusively in the females—more than 40 percent of them."

The findings go beyond clarifying differences in fear behavior among male and female rats. They also point to possibilities for better

treatments for people with PTSD.

Following the fear conditioning, the researchers used a process called "extinction" to suppress the rats' fear response: By playing the tone repeatedly without the shock, a "good" memory may come to replace the bad one. Extinction is akin to exposure therapy for people with PTSD. Exposure therapy works, but not for everyone: it's effective in only about 50 percent of cases, according to numerous studies, and it has a very high dropout rate.

The darters, it turned out, were more successful at extinction than the freezers, suggesting that the neurobiological processes of the males and females differed; the females, it appeared, had an edge. "Females may have developed adaptive strategies to fearful events," says Shansky.

The results raise the question of whether PTSD treatments for women—who develop the disorder twice as frequently as men—should be different from those for men. Even more radically: Might it be possible to develop a therapy that alters the neural circuits of freezers to more closely resemble those of darters?

Shansky expresses the speculation more succinctly: "What if we could turn freezers into darters?" she asks.

More information: Tina M Gruene et al. Sexually divergent expression of active and passive conditioned fear responses in rats, *eLife* (2015). DOI: 10.7554/eLife.11352

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