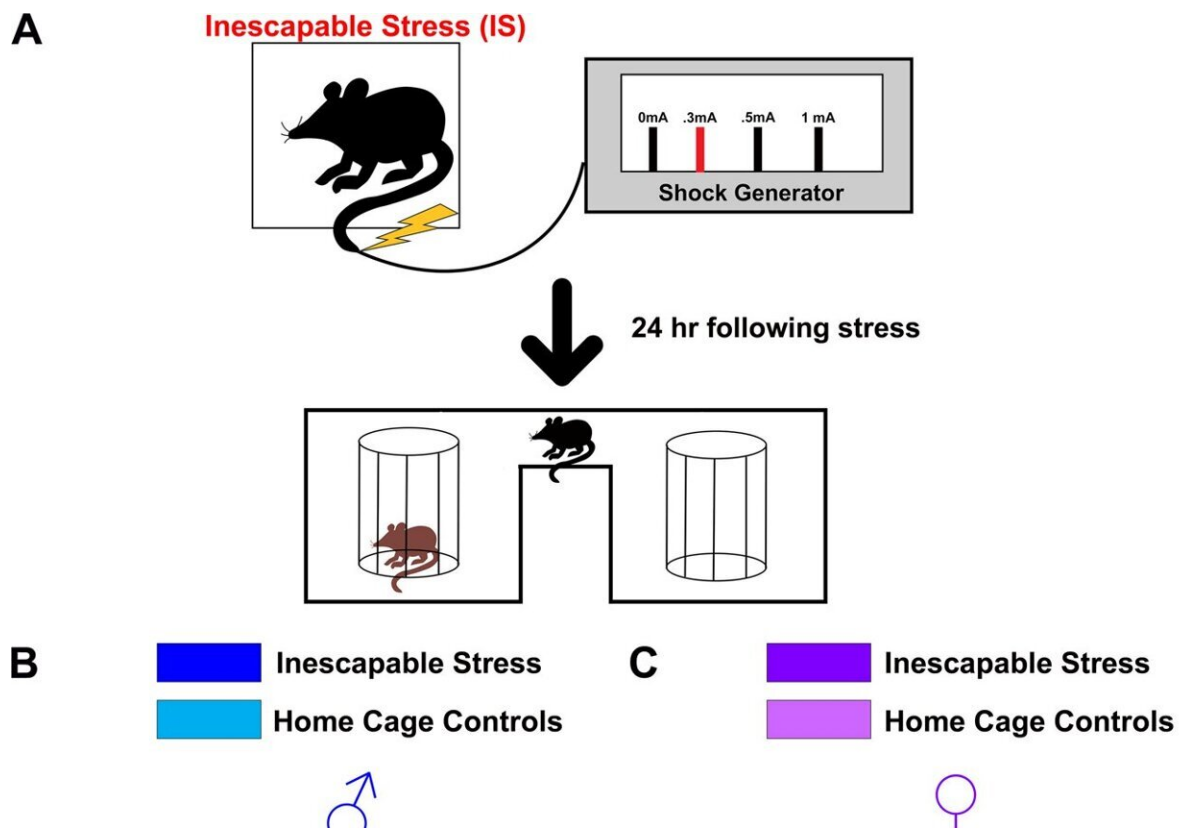


Researchers identify key brain cells in mice underlying stress-related behaviors

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Inescapable stress reduces social exploration in male, but not female, C57BL/6 J mice. Credit: *Molecular Psychiatry* (2022). DOI: 10.1038/s41380-022-01858-3

More than 70% of adults will experience at least one traumatic experience, such as a life-threatening illness or accident, violent assault

or natural disaster, in their lifetimes and nearly a third will experience four or more, according to global data.

While some people who have suffered trauma fully recover, others struggle to find lasting relief.

New CU Boulder research published this week in the journal *Molecular Psychiatry* sheds new light on why that may be.

Researchers found that inescapable stressors impact behavior and the brain differently than stressors that can be controlled, contributing to more generalized and enduring anxiety-like behavior. The study, conducted in mice, also implicates a specific type of brain cell, glutamate cells in the "ventral tegmental area (VTA)," as a key player underlying the impact of stressors.

"Understanding how [stressful experiences](#) shape our brain is critical in order for us to develop new treatments and therapies that can counteract these changes," said co-senior author Michael Baratta, an assistant professor of behavioral neuroscience at CU Boulder. "This study reveals that a little-known population of cells in the brain's reward center is critical in generating the negative consequences of exposure to stress."

Traumatic experiences, the authors note, can lead to a broad range of negative consequences. Some people experience "associative" responses, meaning that thoughts, feelings or external reminders like people, places or things related to the original trauma can prompt anxiety and fear. For instance, a war veteran might flinch at the sound of a car backfiring or fireworks crackling.

Others experience "non-associative" responses, a general aversion to stimuli—including those unrelated to the initial trauma. These kinds of responses can permeate many aspects of life and be harder to treat.

Scientists theorize that associative and non-associative responses to stress may be driven by distinct circuits in the brain. But gold-standard treatments like exposure therapy and [cognitive behavioral therapy](#) tend to only address associative responses.

To better address trauma-related disorders like [post-traumatic stress disorder](#) or PTSD, which impacts 8% of U.S. adults, many believe both circuits must be targeted, said Baratta.

Filling a research gap

To explore this, he and co-senior author David Root, assistant professor of behavioral neuroscience, set out to explore what circumstances, circuits and cells in the brain might drive those hard-to-treat, non-associative responses to trauma.

First, they exposed one group of mice to a stressor that they could easily escape and another to an identical stressor in duration and intensity but with no ability to escape. Behaviorally, the differences were profound. The mice exposed to an inescapable stressor showed more effects on non-associative behavior: Males were less social and less willing to explore and exhibited exaggerated fear; females exhibited general anxiety-like behavior. Meanwhile, mice exposed to a controllable stressor showed little or no effect the next day.

"Having control over some aspect of negative life events has long been associated with resilience in humans," said Root, noting that [animal experiments](#) help scientists better understand the underlying neurobiology at play.

Next, the research team targeted a brain region called the [ventral tegmental area](#) (VTA), often referred to as the brain's reward center due to its rich fabric of reward-associated dopamine-producing cells.

Through laboratory experiments, they found that stress activated a different kind of cells in the VTA known as vesicular glutamate transporter 2 neurons (VGluT2), which produce the chemical messenger glutamate, among other messengers.

When they used cutting-edge molecular tools to temporarily silence a subset of those cells before a stressful event, no negative consequences occurred.

"The mice continued to be social, explore new environments and were very resistant to future stressors," said Root. "It's almost as if the animal didn't experience any stress the day before."

A future 'stress vaccine'?

The study confirms that stress-induced activation of glutamate neurons is required for the development of the more intractable behavioral consequences of trauma. It also suggests that by silencing those cells, the brain can be made more resilient to stress.

But the authors caution that the development of a "magic pill" or "stress vaccine" is a long way off. Notably, both controllable and uncontrollable stress activated glutamate neurons.

"That tells us that they are part of a grander circuit and many more cell types and brain regions are participating in this process," said Root.

The researchers envision a day when soldiers or [emergency room doctors](#) could be given a treatment prophylactically to reduce the activity of such cells before they're exposed to a major stressor, or even after a traumatic event has occurred, to fend off lingering health effects.

"Understanding which neural circuits and cell types contribute to both

associative and nonassociative consequences following stress is a critical step toward developing targeted therapeutics to ameliorate mental health disorders that can result from trauma," said Root.

More information: Dillon J. McGovern et al, Ventral tegmental area glutamate neurons mediate nonassociative consequences of stress, *Molecular Psychiatry* (2022). [DOI: 10.1038/s41380-022-01858-3](https://doi.org/10.1038/s41380-022-01858-3)

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