

How does stress damage memory and cause anxiety disorders?

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The busy life of modern society has made 'stress' a popular term everywhere. Anyone has, is, and will be able to fall into a state of stress. Contrary to what many people think, stress not only causes psychological damage, but also has extremely negative impacts on our physical health.

Chronic stress can cause large bundles of neurons to form in the brain, disrupting memory formation and making us feel fearful of situations that are actually harmless. This may help explain why people with chronic stress often feel threatened in safe environments.

In fact, researchers have long known that stress or trauma can lead to a psychological state of fear of harmless situations. For example, after burning your finger on a hot pan, a state of stress may arise that causes you to feel a fear not only of the pan, but also of the stove or of cooking. This type of generalized fear is common in people with post-traumatic stress disorder (PTSD) and generalized anxiety disorder.



A new study recently published in the journal *Cell* describes how stress disrupts memory formation, and in particular the recall of frightening events. The results could inform the development of treatments for people with PTSD and anxiety disorders.

Essentially, memories are packaged into groups of neurons, called engrams. Engrams are activated when memories are formed. Sheena Josselyn, a neuroscientist at the Hospital for Sick Children in Toronto, Canada, and her colleagues conducted a study to see if stress disrupts engram formation, focusing on a brain region called the amygdala. This is an area involved in the brain's stress and emotional responses.

The study involved a complex three-step experiment in mice. First, Sheena Josselyn and colleagues put several adult mice into a state of stress by injecting them with the stress hormone corticosterone, or by confining them in a small tube for 30 minutes, which increases corticosterone levels in the body.

Next, they placed the mice—some stressed, some not—in a room and played a mid-pitched whistle for 30 seconds—the neutral event. After a break, the mice returned to the room and experienced a high-pitched whistle for 30 seconds, ending with a 2-second electric shock to their feet, meant to mimic a fearful event for them.

To test how mice store memories of these experiences, the researchers placed them in a new environment and played the two sounds mentioned above — observing their reactions.

Unstressed mice stiffened only when they heard the high-pitched whistle, while stressed mice stiffened when they heard both sounds, suggesting that they were unable to distinguish between neutral and fearful events.

The researchers used a variety of techniques to model neural activity in the rodents. They found that, during memory formation, unstressed mice formed small engrams in response to both the buzzer and the foot shock, and these were reactivated only when exposed to the buzzer. But stressed mice formed larger engrams that were reactivated when exposed to both sounds.

Further experiments documented the occurrence of a chain of events in the brain that produced larger engrams in stressed mice. Under normal conditions, specific neurons in the amygdala suppress neuronal activity by releasing a chemical messenger called gamma-aminobutyric acid (GABA). This ensures that a small engram is produced in response to a negative memory. But under stress, excitatory neurons pump neurotransmitters called endocannabinoids into the brain, which bind to glucocorticoid receptors on those inhibitory neurons and prevent them from releasing GABA, resulting in larger engrams. In other words, more neurons can join this exclusive club, Josselyn says.

The team was able to reverse the effects of stress on memory formation using two drugs, one of which is approved for early pregnancy termination, mifepristone. The drugs blocked glucocorticoid receptors or endocannabinoid production, and stressed mice recalled memories in the same way that unstressed mice did. But the researchers cautioned that these drugs would have side effects outside the brain, and would only work if given at the time the memory was formed, making them unlikely to be used in humans, at least for now.

The team is now trying to find out whether engrams can be altered after memories have been formed, or whether there are other ways to minimize the effects of stress on memory.

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