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Adaptive brain response to stress—and its absence—in people with depression

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A new study identifies a novel biomarker indicating resilience to chronic stress. This biomarker is largely absent in people suffering from major depressive disorder, and this absence is further associated with pessimism in daily life, the study finds.

Nature Communications published the research by scientists at Emory University.

The researchers used brain imaging to identify differences in the neurotransmitter glutamate within the medial prefrontal cortex before and after study participants underwent stressful tasks. They then followed the participants for four weeks, using a survey protocol to regularly assess how participants rated their expected and experienced outcomes for daily activities.

"To our knowledge, this is the first work to show that glutamate in the human medial prefrontal cortex shows an adaptive habituation to a new stressful experience if someone has recently experienced a lot of stress," says Michael Treadway, senior author of the study and professor in Emory's Department of Psychology and Department of Psychiatry and Behavioral Science. "Importantly, this habituation is significantly altered in patients with depression. We believe this may be one of the first biological signals of its kind to be identified in relation to stress and people who are clinically depressed."

"Learning more about how acute stress and chronic stress affect the brain may help in the identification of treatment targets for depression," adds Jessica Cooper, first author of the study and a post-doctoral fellow in Treadway's Translational Research in Affective Disorders Laboratory.

The lab focuses on understanding the molecular and circuit-level mechanisms of psychiatric symptoms related to mood disorders, anxiety and decision-making.

It's long been known that stress is a major risk factor for depression, one of the most common and debilitating of mental illnesses. "In many ways, depression is a stress-linked disorder," Treadway says. "It's estimated

that 80 percent of first-time depressive episodes are preceded by significant, chronic life stress."

Around 16 to 20 percent of the U.S. population will meet the criteria for a major depressive disorder during their lifetimes. Experts are predicting rates of depression to climb even further in the wake of the ongoing COVID-19 pandemic. During the pandemic, about four in 10 adults in the United States have reported symptoms of anxiety or depressive disorder, up from one in 10 who reported them in 2019, according to the Kaiser Family Foundation.

"The pandemic has created more isolation for many people, while also increasing the amount of severe stressors and existential threats they experience," Treadway says. "That combination puts a lot of people at high risk for becoming depressed."

Although the link between stress and depression is clearly established, the mechanisms underlying this relationship are not. Experiments with rodents have shown an association between the response of glutamate—the major excitatory neurotransmitter in the mammalian brain—and stress. The role of glutamate in humans with depression, however, has been less clear.

The 88 participants in the current study included people without a mental health disorder and unmedicated patients diagnosed with a major depressive disorder. Participants were surveyed about perceived recent stress in their lives before they underwent experiments using a brain scanning technique known as magnetic resonance spectroscopy.

While in the scanner, participants were required to alternate between performing two tasks that served as acute stressors: Putting their hand up to the wrist in ice water and counting down from the number 2,043 by steps of 17 while someone evaluated their accuracy.

Brain scans before and after the acute stressor measured glutamate in the medial prefrontal cortex, an area of the brain involved with thinking about one's state and forming expectations. Previous research has also found that this brain area is involved in regulating adaptive responses to stress.

Participants submitted saliva samples while in the scanner, allowing the researchers to confirm that the tasks elicited a stress response by measuring the amount of the stress hormone cortisol in the sample.

In healthy individuals, the brain scans revealed that glutamate change in response to stress in the medial prefrontal cortex was predicted by individual levels of recent perceived stress. Healthy participants with lower levels of stress showed increased glutamate in response to acute stress, while healthy participants with higher levels of stress showed a reduced glutamate response to acute stress. This adaptive response was comparatively absent in the patients diagnosed with depression.

"The decrease in the glutamate response over time appears to be a signal, or a marker, of a healthy adaptation to stress," Treadway says. "And if the levels remain high that appears to be a signal for maladaptive responses to stress."

The initial result was strong for the adaptation in healthy participants, but was in a modest sample size, so the researchers decided to see if they could replicate it. "Not only did we get a replication, it was an unusually strong replication," Treadway says.

The experiment also included a group of healthy controls who underwent scanning before and after performing tasks. Rather than stressful tasks, however, the controls were asked to place a hand into warm water or to simply count out loud consecutively. Their glutamate levels were not associated with perceived stress and they did not show a salivary cortisol

response.

To expand their findings, the researchers followed participants for four weeks after scanning. Every other day, the participants reported on their expected and experienced outcomes for activities in their daily lives. The results showed that glutamate changes that were higher than expected based on an individual's level of perceived stress predicted an increased pessimistic outlook—a hallmark for depression.

"We were able to show how a neural response to stress is meaningfully related to what people experience in their daily lives," Cooper says. "We now have a large, rich data set that gives us a tangible lead to build upon as we further investigate how stress contributes to depression."

More information: Jessica A. Cooper et al, Reduced adaptation of glutamatergic stress response is associated with pessimistic expectations in depression, *Nature Communications* (2021). DOI: 10.1038/s41467-021-23284-9

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