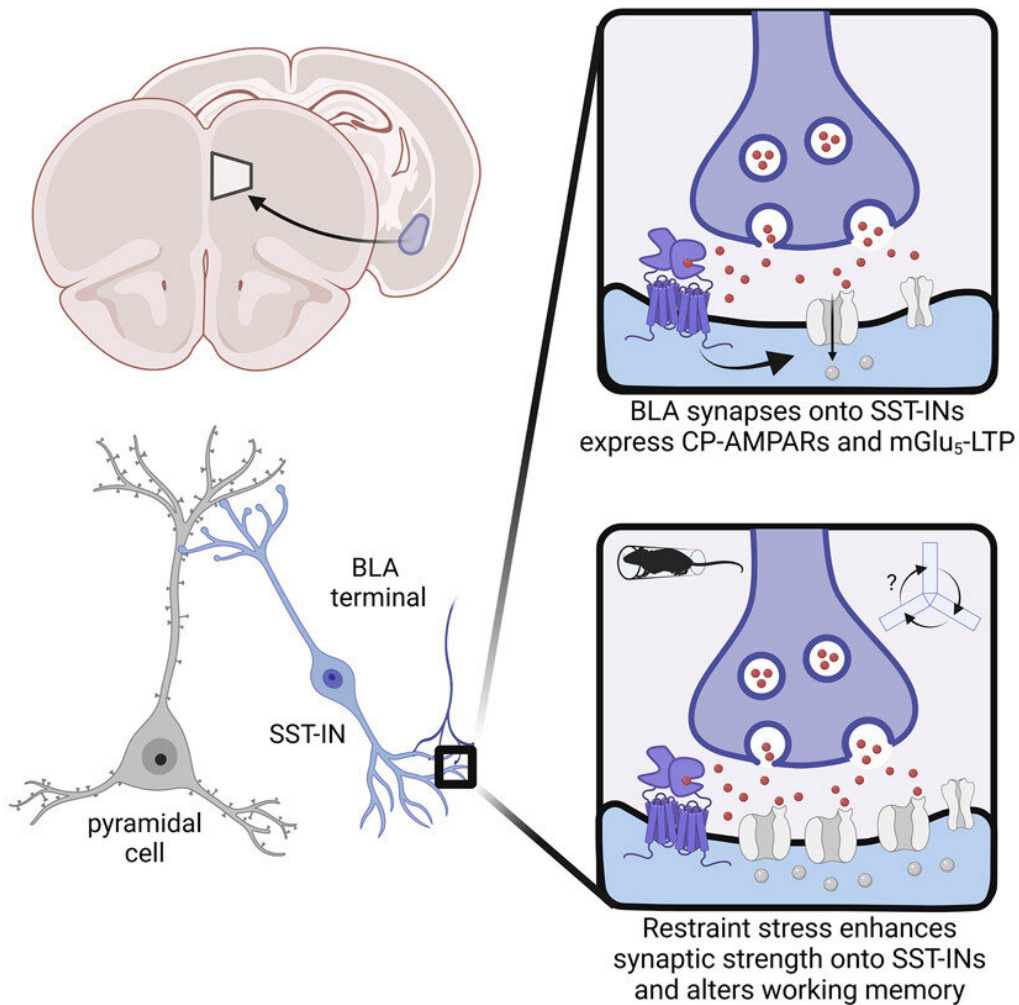


# Understanding the molecules and brain circuits recruited by stressful experience

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Graphical abstract. Credit: DOI: 10.1016/j.neuron.2021.12.027

Stressful experiences can lead to adaptive or detrimental behaviors. Understanding how stress can affect our brains can help understand basic brain function and is also essential to discerning causes and treatments for some diseases. A group of researchers led by Jeffrey Conn, professor of pharmacology at Vanderbilt, explored how specific types of neurons within the prefrontal cortex, the brain area involved in decision-making, mood and motivation, responded to acute stress in models. They found that one type of inhibitory neuron was persistently activated after acute stress, and this research implicated a receptor that has been targeted by the Warren Center for Neuroscience Drug Discovery (WCNDD) for drug development.

"We identified novel plasticity mechanisms that permit [stress](#)-induced changes to behavior. During [acute stress](#), [brain](#) circuits encoding emotion and arousal are rapidly potentiated," said Max Joffe, assistant professor of psychiatry at the University of Pittsburgh and former member of the Conn lab at Vanderbilt. "Through specific inhibitory cells localized to the prefrontal cortex, this plasticity attenuates the activity of cognitive circuits that promote working memory."

According to Conn, "the new understanding provided by these studies has direct implications for the development of potential drugs for treatment of major depression, anxiety and other disorders associated with excessive stress responses."

Multiple factors contributed to the execution of this work. "We used a combination of specific transgenic, optogenetic and pharmacologic tools to examine cell-type specific adaptations in models," Joffe said. "We are deeply thankful and grateful to have had the opportunity to collaborate

with many individuals within the WCNDD and the Vanderbilt Center for Addiction Research. Their efforts were instrumental in this project. We were also excited to work with the Tadross lab at Duke to employ Drugs Acutely Restricted by Tethering (DART) to selectively modulate glutamate receptors in a small group of neurons within the prefrontal cortex."

## Why it matters

In 2021, the American Psychological Association found that more than 80 percent of adults have reported emotions associated with prolonged stress. The research by Conn's team and related efforts is important in seeking out better medications to combat conditions connected with stress and its effect on the brain.

The groups' findings increase the understanding of how stress affects brain function and how it is relevant to the cause of affective disorders, addictions and other diseases, as well as to the basic function of the brain. It may pave the way for future small-molecule medications that directly target stress.

"We hope that these results will help to renew enthusiasm for compounds that inhibit mGlu5 receptors as potential anti-stress, anxiolytic and antidepressant medications. Long term, we hope these studies will provide motivation for targeting somatostatin-expressing interneurons in the prefrontal cortex as cellular targets for new treatments for affective disorders," Joffe said.

The researchers are now interested in understanding how the elements used to conduct this study behave in disease models, particularly chronic stress models and models of alcohol and [drug use](#).

The article, "Acute restraint stress redirects [prefrontal cortex](#) circuit

function through mGlu5 receptor plasticity on somatostatin-expressing interneurons," was published in the journal *Neuron* on Jan. 18.

**More information:** Max E. Joffe et al, Acute restraint stress redirects prefrontal cortex circuit function through mGlu5 receptor plasticity on somatostatin-expressing interneurons, *Neuron* (2022). [DOI: 10.1016/j.neuron.2021.12.027](https://doi.org/10.1016/j.neuron.2021.12.027)

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