Novel neuronal mechanism for stress-induced alteration in behavior identified

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Fluorescent image of PVT neurons. The fox in the background represents the experimental condition where fox odor was used as a stressor for the mice. Credit: Hun-Ren, Laboratory Of Thalamus Research, Laszlo Acsady

Using a rodent stress model, researchers at the Laboratory of Thalamus Research, HUN-REN Institute of Experimental Medicine discovered a

sustained increase in neural activity that persisted for several days after exposure to a strongly stressful event in a thalamic nucleus called paraventricular thalamus (PVT).

Prolonged elevation of PVT activity was paralleled by restlessness during wakefulness, disturbed behavior before falling asleep, and prolonged sleep onset. If the PVT activity was selectively inhibited after the stress event for only one hour, the sustained increase in PVT activity did not take place and the behavior of the mice remained normal after the stress event during the ensuing days. The paper is published in the journal *PLOS Biology*.

Increased spontaneous activity that persists for days has never been described in the brain. The brain typically has robust mechanisms to reduce excessive excitatory activity. Increased excitation is always paralleled by a compensatory increase in inhibition. Even in the epileptic brain, neuronal activity between the seizures is largely normal because of increased inhibition.

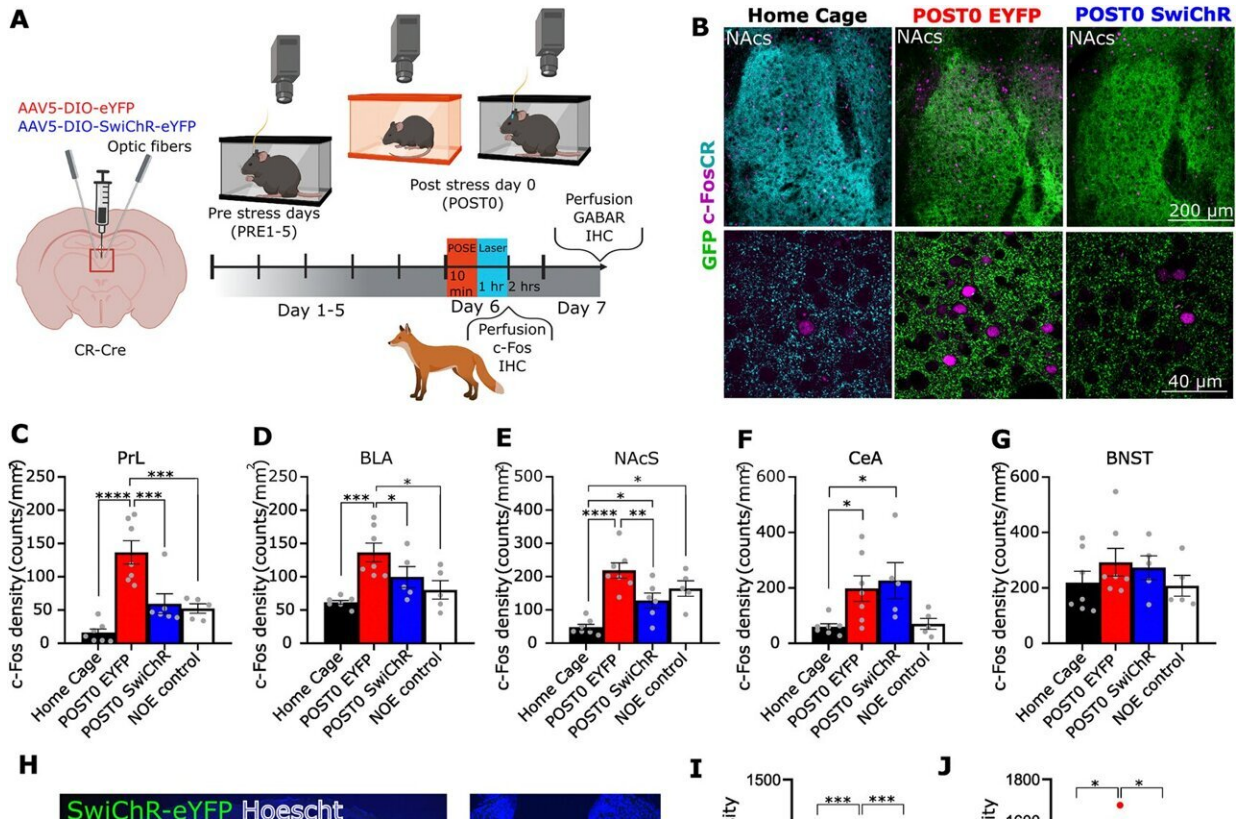
The present data demonstrate that persistently increased activity can still take place under special circumstances in special brain regions. The data highlight a mechanism that allows us to alter the state of the brain for prolonged periods after exposure to a single salient event. The results also show that this increase in neuronal activity is reversible, suggesting that the effect of a stressful event can be ameliorated possibly by natural mechanisms as well.

The heightened activity was recorded in the PVT, a uniquely organized cluster of neurons in the thalamus. This was no coincidence: the PVT acts as a "hub" where inputs from brain areas encoding stress, alertness and motivation converge before being relayed to the cortex as a fast glutamatergic neuronal message.

The integrated message is projected to all major forebrain centers (amygdala, prefrontal cortex, hippocampus, nucleus accumbens) that control behavior. No other brain region is known to display similar connectional properties. Thus, PVT acts like a real bottleneck in the brainstem-forebrain communication, an integrator of stress signals.

An earlier study by the same research group demonstrated that the organization of PVT is very similar in mice and humans. PVT contains the same cell type in both species and receives similar selective inputs from the brainstem and the hypothalamus. This shows that the brain center specialized to transfer emotional and arousal signals to the forebrain is evolutionarily highly conserved.

In the mice model, the researchers exposed the animals to an ecologically relevant stressor, the scent of a predator (fox) for 10 minutes. The ensuing behavioral phenotype was very similar to the symptom clusters of acute stress disorder (negative mood, avoidance, increased arousal, sleep problems). This validates the present approach as a potentially relevant animal model to study the initial changes in the brain after a significantly stressful event.



Role of PVT/CR+ neurons in stress-induced molecular changes. Credit: *PLOS Biology* (2025). DOI: 10.1371/journal.pbio.3002962

Implications for treating stress disorders

A traumatic experience or a major stressful event can lead to lasting, and in some cases lifelong, changes in behavior. Although this phenomenon is well known, its neurological underpinnings are not yet understood, and effective treatments are still lacking.

An assault in the street, an accident, a family tragedy, or an ordeal causes lasting changes in behavior in around 20% of individuals who experience such events. Researchers distinguish between the early, acute phase (up to 30 days after the stressor) and the later phase (after 30 days, in cases

of post-traumatic stress disorder, PTSD) of the disease. Symptoms are similar in both phases.

One of the best-known symptoms of PTSD is the frequent recurrence of traumatic memories in inappropriate situations. In addition to these intermittent symptoms, there can be persistent ones that significantly affect mood and behavior. Examples of such symptoms include restlessness, difficulty falling asleep, emotional instability, and withdrawal.

Many studies have investigated how the brain encodes and retrieves memories but it still remains less clear what neural mechanisms underlie the persistent emotional changes following a trauma. Researchers know that during the encoding and retrieval of memories, brief changes occur in the activity of neurons that store these memories.

However, when the event is not recalled, the brain's memory trace remains in a "dormant" state: neural activity is low and unchanged. Can brief fluctuations in activity related to memory recalls lead to persistent emotional changes? Or is the latter governed by independent mechanisms? This is a crucial question because currently the main treatments for PTSD focus on extinguishing memories, but these approaches are not very effective.

The present data point to a mechanism that is independent of the memory trace, displays persistent changes after the stress event and is causally related to the stress-induced alteration of behavior. This mechanism could pave the way for new therapies for treating stress-related issues.

By modulating PVT activity, treatments could be developed that effectively address stress-induced anxiety and trauma-related disorders. A deeper understanding of these long-term neural changes could also

contribute to the development of targeted therapies aimed at alleviating stress-related behavioral disorders.

Finally, the researchers found that the short, one-hour long inhibition of PVT remained significantly effective even when applied five days after the stressful event. This finding extends the potential therapeutic time window in which a treatment based on these findings could be effective.

More information: Anna Jász et al, Persistently increased post-stress activity of paraventricular thalamic neurons is essential for the emergence of stress-induced alterations in behaviour, *PLOS Biology* (2025). DOI: 10.1371/journal.pbio.3002962

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