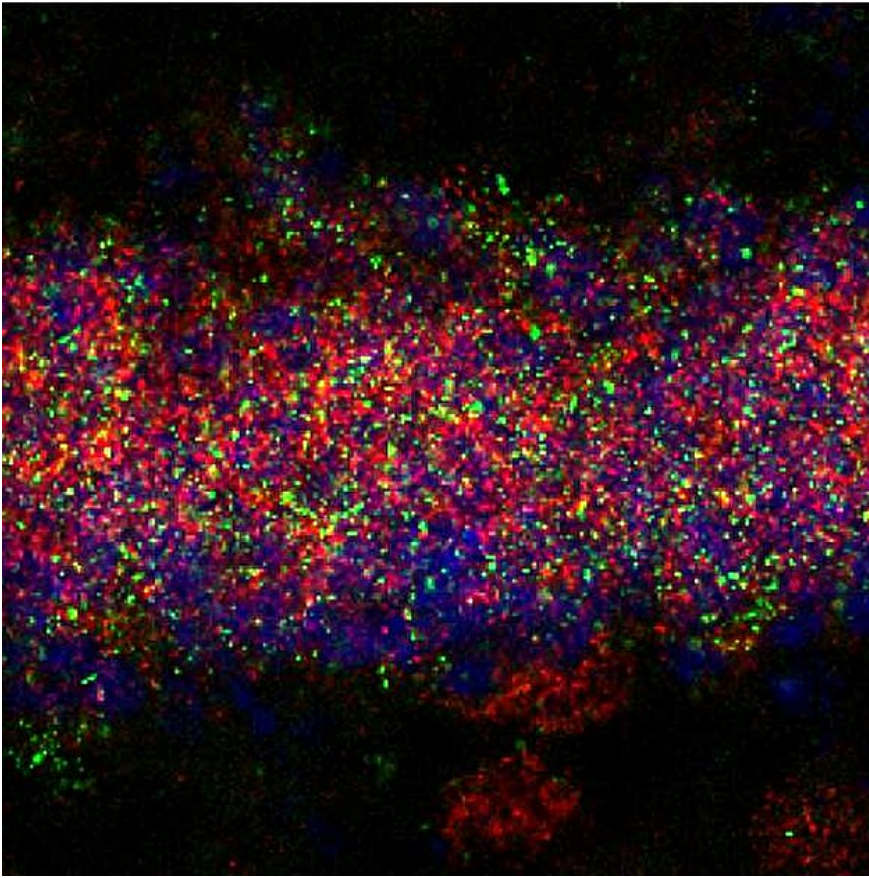
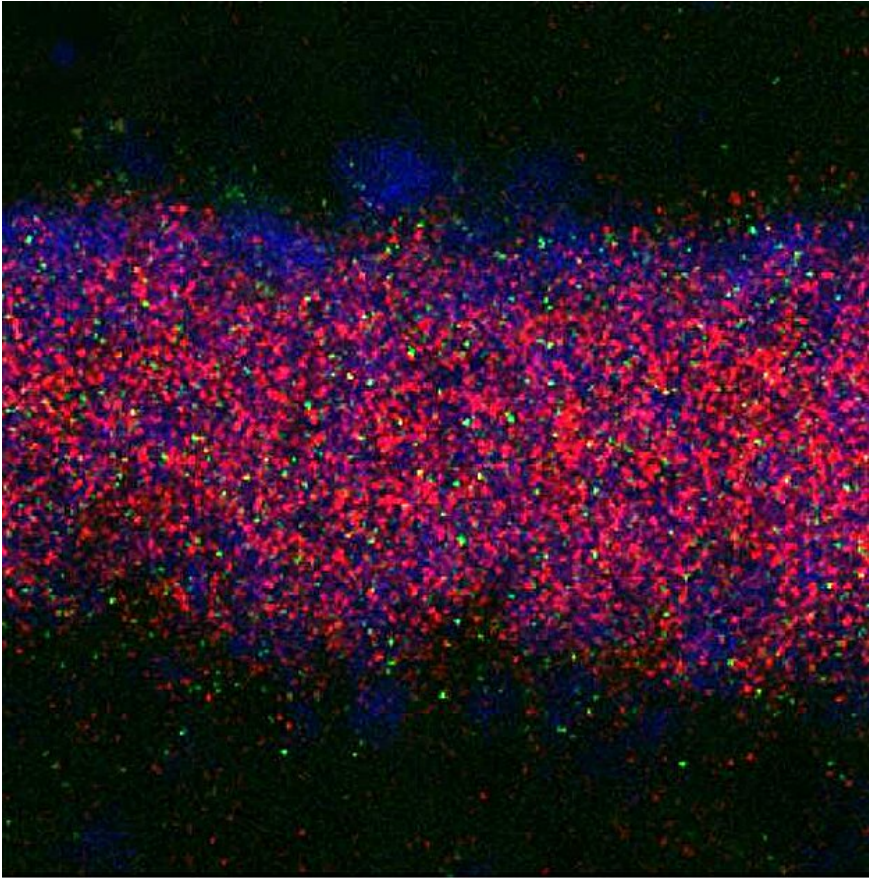


Researchers identify traces of trauma in the young brain and suggest how to erase them

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Bullying produced different effects on neurons in the hippocampus of adult mice—depending on whether these mice had been exposed to stress in infancy (bottom) or not (top). The images reveal some of the most striking differences in gene expression (green) in the excitatory (red) neurons. Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.adj3793

The images of Israeli child hostages being freed from Hamas captivity are heartwarming, but for most of these children, the release is just the start of a long rehabilitation process. Countless studies have shown that exposure to warfare, abuse and other traumatic events at a young age significantly raises the risk of ill health, social problems and mental health issues later in life.

Now, a new study by researchers at the Weizmann Institute of Science provides a reason for optimism. In research conducted on [mice](#), [published](#) Dec. 1 in *Science Advances*, a team headed by Prof. Alon Chen discovered brain mechanisms that go awry as a result of exposure to [trauma](#) in infancy and showed that these changes may be reversible if treated early.

Our brains have a wonderful quality known as plasticity, the ability to change throughout our lives. As may be expected, in our early years, when the brain is still developing, it is at peak plasticity. This manifests in, for example, the aptitude for learning languages, but this also entails a heightened sensitivity to [traumatic events](#), which are liable to leave a scar that only intensifies with age. Many studies provide evidence for the latter effect, but very little is known about the way that exposure to trauma at a young age affects the different kinds of brain cells and the communication between them in adulthood.

Chen's laboratory in Weizmann's Brain Sciences Department focuses on the molecular and behavioral aspects of the response to stress. In [previous studies](#), Chen's team examined how stress during pregnancy affects mouse offspring when they reach maturity. In the current research, the scientists, led by Dr. Aron Kos, studied how trauma experienced shortly after birth affects mouse pups later in life.

To advance the understanding of this topic, the researchers pulled together the strengths of Chen's lab: its expertise in exploring the brain's molecular processes at the highest possible resolution, using genetic sequencing on the level of individual cells; the ability to use cameras to track dozens of behavioral variables in a rich social environment intended to recreate natural living conditions; and the ability to process the massive quantities of data generated in this environment, using machine learning and artificial intelligence tools.

This comprehensive behavioral mapping revealed that mice exposed after birth to a traumatic event—in the case of this study, being neglected by their mothers—displayed a variety of behaviors indicating that they found themselves at the bottom of the dominance hierarchy.

"Equivalent behaviors in humans might include high levels of introversion, social anxiety and having an avoidant personality, all known to be characteristic of posttrauma," says Dr. Juan Pablo Lopez, a former postdoctoral fellow in Chen's joint laboratory at Weizmann and the Max Planck Institute of Psychiatry in Munich, and today head of a research group in the Department of Neuroscience at the Karolinska Institute in Stockholm.

In the next stage of the study, the researchers exposed some of the adult mice that had experienced trauma in infancy to a stressful social situation: bullying by other mice. Ultimately, they created four groups of adult mice: those that had not been exposed to any trauma; those that had

not been exposed to trauma in infancy but were subjected to bullying as adults; mice that were exposed to trauma only in infancy; and mice that were exposed to both trauma in infancy and bullying as adults.

To find out how exposure to early trauma disrupts the brain and what happens as a result of this in adulthood, the researchers carried out a meticulous comparison of the four groups, using RNA sequencing at the single-cell level in the hippocampus, a brain area known to play an important role in social functioning.

The comparison revealed that early trauma left a mark on different types of cells, primarily affecting gene expression in two subpopulations of neurons, those belonging to the glutamatergic excitatory system and those belonging to the GABA inhibitory system. This effect was especially strong in mice that had been exposed to both trauma in infancy and bullying as adults.

Cells in the brain communicate with one another by means of electrical signals, which can be excitatory, that is, stimulating, or inhibitory. An excitatory signal encourages communication between brain cells, whereas an inhibitory signal represses it, like the gas and brake pedals in a car. Normal brain functioning requires a balance between the excitatory and inhibitory signals, which is lacking in many psychiatric disorders.

One of the ways of assessing the brain's electrical activity and the balance between excitatory and inhibitory signals is through electrophysiological measurements. Such measurements, performed in the hippocampus of the mice by Dr. Julien Dine, a former staff scientist at the Weizmann Institute and currently a pharmaceutical electrophysiologist, supported the molecular findings: Exposure to trauma in early childhood disrupted the balance between excitatory and inhibitory signals in adulthood.

Having discovered a brain mechanism that is disrupted in adulthood as a result of early trauma—and having identified this disruption as an imbalance between the excitatory and inhibitory signals—the researchers tried to find a way to fix it. During a brief treatment window shortly after the early trauma, they gave the mice a well-known antianxiety drug—diazepam, known commercially as Valium—which affects the GABA inhibitory system.

This short course of treatment led to results that were nothing less than stunning: The treated mice were able to fully or almost fully avoid the behavioral future that awaited them and were no longer at the foot of the social ladder. "Understanding the molecular and functional mechanisms allowed us to neutralize the negative behavioral impact of trauma with a drug given shortly after exposure to traumatic incidents," Kos explains. "This certainly should not be seen as a recommendation to treat young trauma patients with drugs, but our findings do highlight the importance of early treatment for successful rehabilitation."

Intense, ongoing stress can, at any age, contribute to disease, from psychiatric disorders to obesity and diabetes. But in the first years of life—and also in the womb—such stress can have dramatic ramifications. "The wars in Israel, Ukraine, Sudan and elsewhere, and the unprecedented global refugee crisis that is caused, in part, by climate change, alongside an increased understanding of the long-term harm caused by exposure to war and violence at a young age—all these highlight the need for better rehabilitation capabilities," says Chen.

"Our new study identifies a key brain mechanism that is especially sensitive to childhood trauma. But the most exciting part is the prospect of using the plasticity of the young [brain](#) to help it recover, avoiding the toll this trauma can exact in adulthood."

More information: Aron Kos et al, Early life adversity shapes social

subordination and cell type–specific transcriptomic patterning in the ventral hippocampus, *Science Advances* (2023). [DOI: 10.1126/sciadv.adj3793](https://doi.org/10.1126/sciadv.adj3793)

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