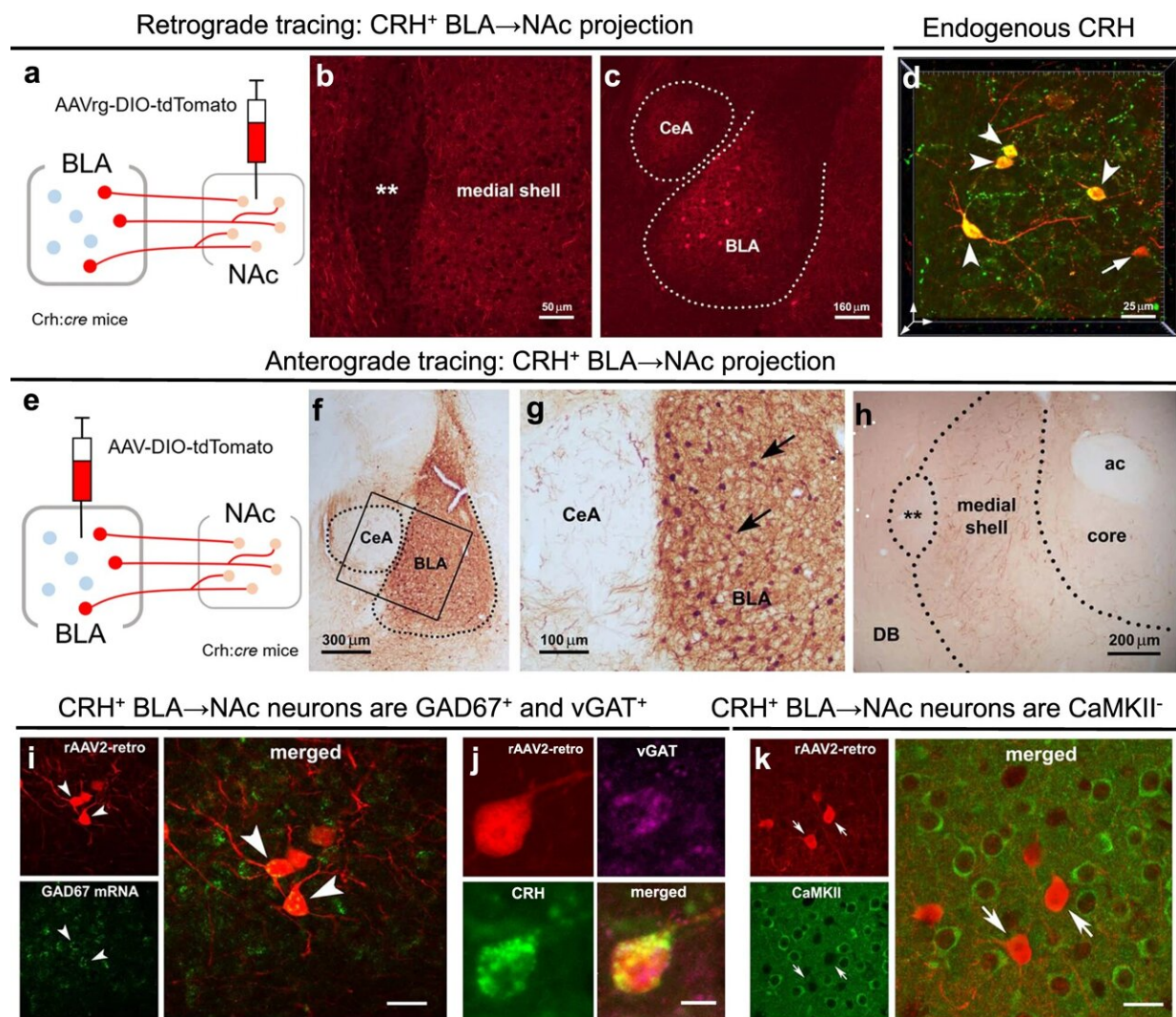


Early-life stress can disrupt maturation of brain's reward circuits, promoting disorders

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A projection of CRH/GABA neurons in the medial BLA to the medial NAc shell. **a–c** Retrograde tracing of CRH⁺ neuronal inputs to medial NAc shell of CRH-ires-CRE mice. **a** Schematic of construct and injection location of

AAV2-retro-CAG-FLEX-tdTomato-WPRE virus that permits retrograde access to projection neurons providing afferent inputs to NAc. **b** Example confocal micrograph of locally infected CRH⁺ axon terminals in medial NAc shell. **c** Retrograde tracing identifies the medial BLA as a robust source of CRH⁺ NAc inputs. **d** 3D image (z-stack; 0.5 μ m steps) confirmed localization in the BLA of AAV-retro infected cells (red) that co-express endogenous CRH (green); dual labeled neurons = yellow. **e–g** Anterograde tracing of CRH⁺ axonal projections from BLA to medial NAc shell. **e**, The AAV1-DIO-tdTomato construct and the viral genetic experimental design. **f** Virus injection is confined to the BLA, **g** and absent from the central amygdala (CeA), shown by selective expression of tdTomato in BLA CRH⁺ neurons. **h** BLA-origin CRH⁺ axons and terminals in the medial NAc shell. **i–k** Virus injection into the medial NAc shell retrogradely infected somata in the BLA. **i** Combined fluorescence in situ hybridization (FISH) and immunostaining with GAD67 mRNA in CRH⁺ cells in the BLA. Arrowheads point to co-localized GAD67 mRNA and virus-reporter labeling. **j** a BLA \rightarrow NAc cell (red) co-expresses endogenous CRH (green) and vGAT (magenta), but **k** does not co-express the glutamatergic marker CaMKII. ** = Major Island of Calleja, ac anterior commissure, DB diagonal band. Scale bars in **i** and **k** = 10 μ m. To confirm findings, virus injections, projection assessment, and immunohistochemistry were assessed in mice from at least two independent litters. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-36780-x

A new brain connection discovered by University of California, Irvine researchers can explain how early-life stress and adversity trigger disrupted operation of the brain's reward circuit, offering a new therapeutic target for treating mental illness. Impaired function of this circuit is thought to underlie several major disorders, such as depression, substance abuse and excessive risk-taking.

In an article recently published online in *Nature Communications*, Dr. Tallie Z. Baram, senior author and UCI Donald Bren Professor and Distinguished Professor in the Departments of Anatomy &

Neurobiology, Pediatrics, Neurology and Physiology & Biophysics, and Matt Birnie, lead author and a postdoctoral researcher, describe the cellular changes in the brain's circuitry caused by exposure to adversity during childhood.

"We know that early-life stress impacts the brain, but until now, we didn't know how," Baram said. "Our team focused on identifying potentially stress-sensitive brain pathways. We discovered a new pathway within the reward circuit that expresses a molecule called corticotropin-releasing hormone that controls our responses to stress. We found that adverse experiences cause this brain pathway to be overactive."

"These changes to the pathway disrupt reward behaviors, reducing pleasure and motivation for fun, food and sex cues in mice," she said. "In humans, such behavioral changes, called 'anhedonia,' are associated with emotional disorders. Importantly, we discovered that when we silence this pathway using [modern technology](#), we restore the brain's normal reward behaviors."

Researchers mapped all the CRH-expressing connections to the nucleus accumbens, a pleasure and motivation hub in the brain, and found a previously unknown projection arising from the basolateral amygdala. In addition to CRH, projection fibers co-expressed gamma-aminobutyric acid. They found that this new pathway, when stimulated, suppresses several types of reward behaviors in male mice.

The study involved two groups of male and female mice. One was exposed to adversity early in life by living for a week in cages with limited bedding and nesting material, and the other was reared in typical cages. As adults, the early adversity-experiencing male mice had little interest in sweet foods or sex cues compared to typically reared mice. In contrast, adversity-experiencing females craved rich, sweet food.

Inhibiting the pathway restored normal reward behaviors in males, yet it had no effect in females.

"We believe that our findings provide breakthrough insights into the impact of early-life adversity on [brain development](#) and specifically on control of reward behaviors that underlie many emotional disorders. Our discovery of the previously unknown circuit function of the [basolateral amygdala-nucleus accumbens brain pathway](#) deepens our understanding of this complex mechanism and identifies a significant new therapeutic target," Baram said.

"Future studies are needed to increase our understanding of the different and sex-specific effects of early-life adversity on [behavior](#)."

More information: Matthew T. Birnie et al, Stress-induced plasticity of a CRH/GABA projection disrupts reward behaviors in mice, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-36780-x](https://doi.org/10.1038/s41467-023-36780-x)

Provided by University of California, Irvine

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