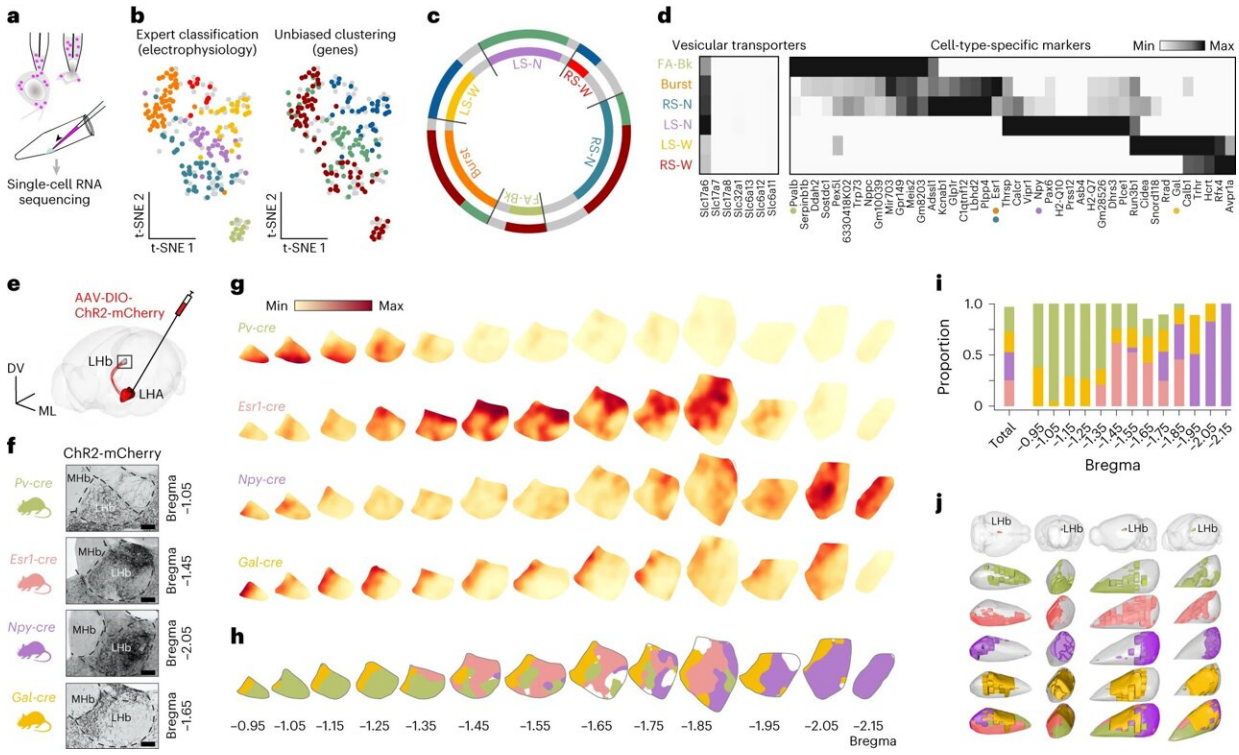
Chronic stress-related neurons identified

June 22 2023



Discrete organization of genetically targeted LHA–LHb pathways. **a**, Schematic of Patch-seq showing somatic harvesting of retrobead-labeled LHA–LHb neurons. **b**, t-SNE plots of all recorded LHA–LHb neurons (n_{neuron} = 230, n_{mice} = 46 WT, same neurons as in Fig. 1). The cell type identify of neurons collected for Patch-seq are color coded based on electrophysiology (expert classification; left), or gene expression (unbiased clustering; right). n = 163 collected neurons; FA-Bk, n_{neuron} = 12; Burst, n_{neuron} = 42; RS-N, n_{neuron} = 35; LS-N, n_{neuron} = 35; LS-W, n_{neuron} = 28; RS-W, n_{neuron} = 11 and n_{mice} = 46 WT. Gray neurons, recorded but not collected. **c**, Comparison of electrophysiological (expert classification as in **b**, left) versus gene expression classification (unbiased clustering as in **b**, right) of LHA–LHb neurons (colored as in **b**). **d**, Heatmap of genes with

differential expression in the electrophysiologically defined LHA–LHb neuron types (right). Expression of vesicular transporters in the LHA–LHb neuron types (left). Colored dots represent genetic markers employed for subsequent cell-type-specific targeting. **e**, Experimental strategy for anterograde labeling of LHA–LHb axon terminals. **f**, Representative images of virally labeled LHA–LHb axon terminals in the mouse *cre* lines used for targeting specific LHA–LHb pathways (*Pv-cre*, *Esr1-cre*, *Npy-cre* and *Gal-cre* mice, respectively). Brain section with peak terminal density is shown. **g**, Heatmaps of the axon terminal density in the LHb for the four genetically targeted LHA–LHb pathways. **h**, Visualization of the topographical organization of the pathway-specific projection fields in the LHb. Colors as in **g**, white is not assigned to a specific pathway (Methods). **i**, Proportion of the LHb area targeted by the distinct LHA–LHb pathways, plotted along the A-P axis. Left bar, cumulative targeting of LHb by the four LHA–LHb pathways. **j**, Three-dimensional reconstructions (four different orientations) of the LHb projection fields of the four LHA–LHb pathways. n_{neuron} = number of neurons, n_{mice} = number of mice. All data were acquired in male mice. Scale bar, 100 μm (**f**). See also Extended Data Figs. 3 and 4. MHb, medial habenula. Credit: *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01367-8

Researchers at Karolinska Institutet in Sweden have identified a group of nerve cells in the mouse brain that are involved in creating negative emotional states and chronic stress. The neurons, which have been mapped with a combination of advanced techniques, also have receptors for estrogen, which could explain why women as a group are more sensitive to stress than men. The study is published in *Nature Neuroscience*.

Just which networks in the brain give rise to negative emotions (aversion) and chronic stress have long been unknown to science.

By using a combination of advanced techniques, such as Patch-seq, large-scale electrophysiology (Neuropixels) and optogenetics, KI researchers

Konstantinos Meletis and Marie Carlén and their team have been able to map out a specific neuronal pathway in the mouse brain leading from the hypothalamus to the habenula that controls aversion.

The researchers used optogenetics to activate the pathway when the mice entered a particular room, and found that the mice soon started to avoid the room even though there was nothing in it.

Opens the way for novel treatments for depression

"We discovered this connection between the hypothalamus and the habenula in a previous study but didn't know what types of neurons the pathway was made up of," says Konstantinos Meletis, professor at the Department of Neuroscience, Karolinska Institutet. "It's incredibly exciting to now understand what type of neuron in the pathway controls aversion. If we can understand how negative signals in the brain are created, we can also find mechanisms behind affective diseases like depression, which will open the way for novel drug treatments."

The study was led by three postdocs at the same department, Daniela Calvigioni, Janos Fuzik and Pierre Le Merre, and as Professor Meletis explains, is an example of how scientists can use advanced techniques to identify neuronal pathways and neurons that control emotions and behavior.

Sensitive to estrogen levels

Another interesting discovery is that the neurons linked to aversion have a receptor for estrogen, making them sensitive to estrogen levels. When male and female mice were subjected to the same type of unpredictable mild aversive events, the female mouse developed a much more lasting stress response than the male.

"It has long been known that anxiety and depression are more common in women than in men, but there hasn't been any biological mechanism to explain it," says Marie Carlén, professor at the Department of Neuroscience. "We've now found a mechanism that can at least explain these sex differences in mice."

More information: Le Merre, P. et al. Esr1+ hypothalamic-habenula neurons shape aversive states, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01367-8.
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Provided by Karolinska Institutet