Overwhelmed? Your astrocytes can help with that

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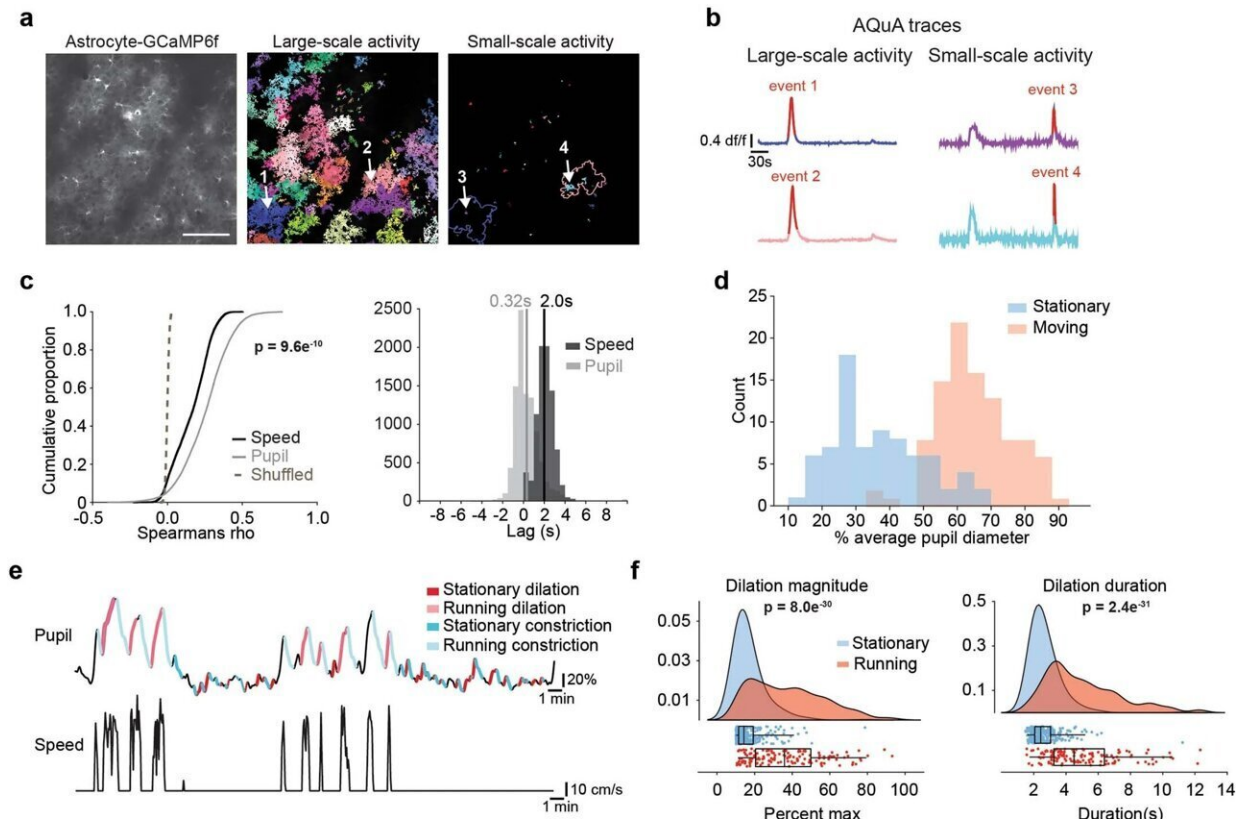

Dissection of astrocyte Ca^{2+} and behavioral state. (a) Representative 2P mean projection image from one ten-minute recording of in vivo astrocyte GcaMP6f (left, scale bar = 100 μm). AQuA detected both large (middle) and small (right) astrocyte Ca^{2+} events within the entire movie, even when they were spatially overlapping. Arrows indicate two pairs of spatially overlapping events (arrows 1 and 3, and arrows 2 and 4).(b) Traces from the AQuA events shown in (a), with the time period of the AQuA-detected event highlighted in red. (c) Related to Fig. 1c: Individual astrocyte Ca^{2+} events correlated better with pupil diameter

(left, n = 1.2e^4 Ca^{2+} events, One-sided Kruskal-Wallis test) and had a shorter lag with pupil diameter than wheel speed (right, pupil n = 9.6e^3, wheel n = 8.3e^3, rank-sum test). (d) Related to Fig. 1d: average pupil diameter during movement (n = 100) and stationary periods (n = 76). (e) Classification of behavioral state by both pupil diameter and movement. (f) Pupil dilation is smaller (left) and shorter (right, rank-sum tests) during stationary periods (n = 261 dilations, blue) compared with movement-associated dilations (n = 136 dilations, red, boxplots show median and IQR with whiskers to 1.5 * IQR, two-sided Rank Sum test). (g) Related to Fig. 1l: Left: Movement duration (n = 104) was related to the maximum wheel speed (top) and pupil diameter (middle), but not to the maximum astrocyte Ca^{2+} (bottom). Right: the latency to the maximum wheel speed (top), pupil diameter (middle), and astrocyte Ca^{2+} (bottom) were strongly linked to movement duration. (h) Heatmap summary of the r^2 between the latencies in (g) right, and movement bout duration. Credit: *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01284-w

A brimming inbox on Monday morning sets your head spinning. You take a moment to breathe and your mind clears enough to survey the emails one by one. This calming effect occurs thanks to a newly discovered brain circuit involving a lesser-known type of brain cell, the astrocyte. According to new research from UC San Francisco, astrocytes tune into and moderate the chatter between overactive neurons.

This new brain circuit, described March 30, 2023 in *Nature Neuroscience*, plays a role in modulating attention and perception, and may hold a key to treating attention disorders like ADHD that are neither well understood nor well treated, despite an abundance of research on the role of neurons.

Scientists found that noradrenaline, a neurotransmitter that can be thought of as adrenaline for the brain, sends one chemical message to neurons to be more alert, while sending another to astrocytes to quiet

down the overactive neurons.

"When you're startled or overwhelmed, there's so much activity going on in your brain that you can't take in any more information," said Kira Poskanzer, Ph.D., an assistant professor of biochemistry and biophysics and senior author of the study.

Until this study, it was assumed that brain activity just quieted down with time as the amount of noradrenaline in the brain dissipated.

"We've shown that in fact, it's astrocytes pulling the handbrake and driving the brain to a more relaxed state," Poskanzer said.

A missing piece

Astrocytes are star-shaped cells woven between the brain's neurons in a grid-like pattern. Their many star arms connect a single astrocyte to thousands of synapses, which are the connections between neurons. This arrangement positions astrocytes to eavesdrop on neurons and regulate their signals.

These cells have traditionally been thought of as simple support cells for neurons, but new research in the last decade shows that astrocytes respond to a variety of neurotransmitters and may have pivotal roles in neurologic conditions like Alzheimer's disease.

Michael Reitman, Ph.D., first author of the paper who was a graduate student in Poskanzer's lab when he did the research, wanted to know whether astrocyte activity could explain how the brain recovers from a burst of noradrenaline.

"It seemed like there was a central piece missing in the explanation of how our brains recover from that acute stress," said Reitman. "There are

these other cells right nearby which are sensitive to noradrenaline and might help coordinate what the neurons around them are doing."

Gatekeepers of perception

The team focused on understanding perception, or how the brain processes sensory experiences, which can be quite different depending on what state a person (or any other animal) is in at the time.

For example, if you hear thunder while cozying up indoors, the sound may seem relaxing and your brain may even tune it out. But if you hear the same sound out on a hike, your brain may become more alert and focused on safety.

"These differences in our perception of a sensory stimulus happen because our brains are processing the information differently, based on the environment and state we're already in," said Poskanzer, who is also a member of the Kavli Institute for Fundamental Neuroscience.

"Our team is trying to understand how this processing looks different in the brain under these different circumstances," she said.

Completing the puzzle

To do that, Poskanzer and Reitman looked at how mice responded when given a drug that stimulates the same receptors that respond to noradrenaline. They then measured how much the mice's pupils dilated and looked at brain signals in the visual cortex.

But what they found seemed counterintuitive: rather than exciting the mice, the drug relaxed them.

"This result really didn't make sense, given the models we have, and that led us down the path of thinking that another cell type could be important here," Poskanzer said. "It turns out that these two things are yoked together in a feedback circuit. Given how many neurons each astrocyte can talk to, this system makes them really important and nuanced regulators of our perception."

The researchers suspect that astrocytes may play a similar role for other neurotransmitters in the brain, since being able to transition smoothly from one brain state to another is essential for survival.

"We didn't expect the cycle to look like this, but it makes so much sense now," Poskanzer said. "It's so elegant."

Additional authors on the paper include Vincent Tse, Drew D. Willoughby, Alba Peinado, Bat-Erdene Myagmar, and Paul C. Simpson, Jr. of UCSF, Xuelong Mi and Guoqiang Yu of Virginia Polytechnic Institute and State University, and Alexander Aivazidis and Omer A. Bayraktar of the Wellcome Sanger Institute.

More information: Michael E. Reitman et al, Norepinephrine links astrocytic activity to regulation of cortical state, *Nature Neuroscience* (2023). DOI: 10.1038/s41593-023-01284-w

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