How the brain responds to surprising events

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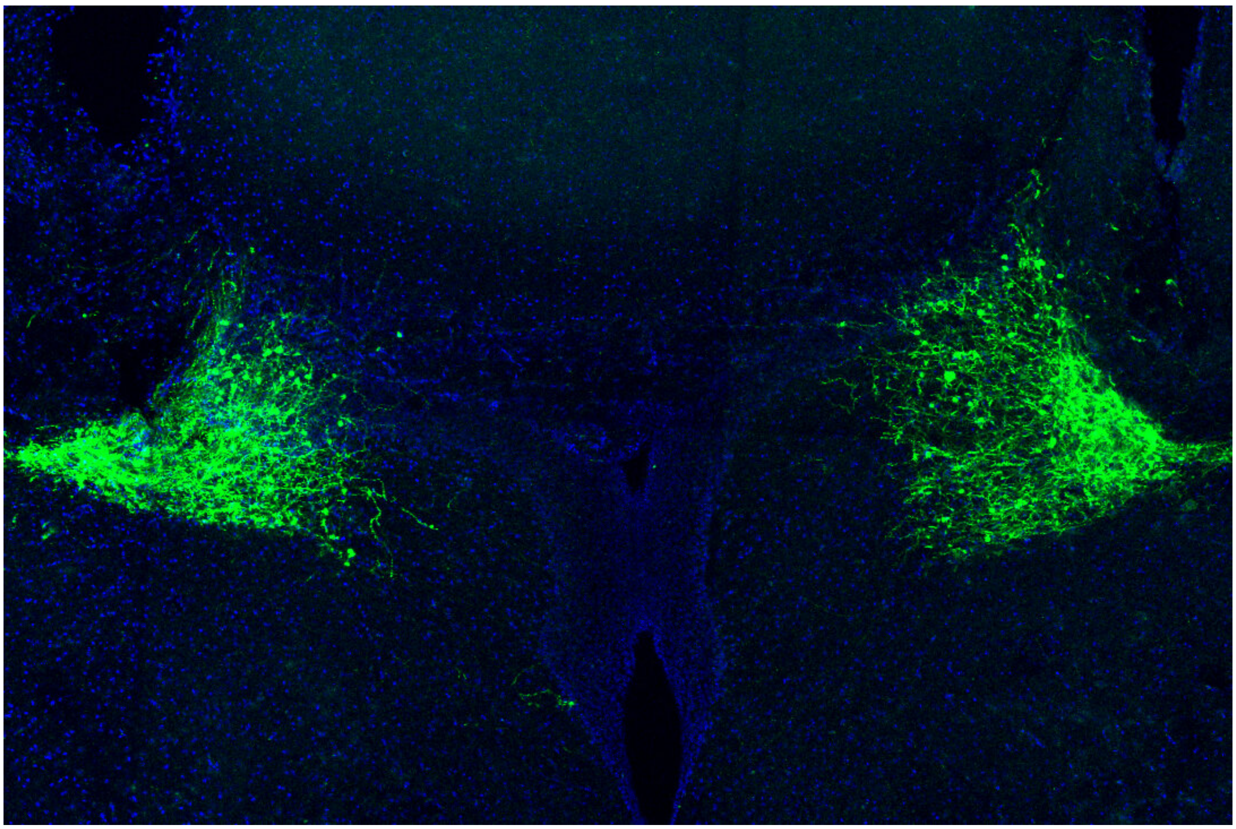

Most of the brain's noradrenaline is produced by the two locus coeruleus nuclei, one in each brain hemisphere. The neurons of the locus coeruleus are labeled with green fluorescent protein. Credit: Gabi Drummond

When your brain needs you to pay attention to something important, one way it can do that is to send out a burst of noradrenaline, according to a new MIT study.

This neuromodulator, produced by a structure deep in the brain called the locus coeruleus, can have widespread effects throughout the brain. In a study of mice, the MIT team found that one key role of noradrenaline, also known as norepinephrine, is to help the brain learn from surprising outcomes.

"What this work shows is that the locus coeruleus encodes unexpected events, and paying attention to those surprising events is crucial for the brain to take stock of its environment," says Mriganka Sur, the Newton Professor of Neuroscience in MIT's Department of Brain and Cognitive Sciences, a member of MIT's Picower Institute for Learning and Memory, and director of the Simons Center for the Social Brain.

In addition to its role in signaling surprise, the researchers also discovered that noradrenaline helps to stimulate behavior that leads to a reward, particularly in situations where there is uncertainty over whether a reward will be offered.

Sur is the senior author of the new study, which appears today in *Nature*. Vincent Breton-Provencher, a former MIT postdoc who is now an assistant professor at Laval University, and Gabrielle Drummond, an MIT graduate student, are the lead authors of the paper.

Modulating behavior

Noradrenaline is one of several neuromodulators that influence the brain, along with dopamine, serotonin, and acetylcholine. Unlike neurotransmitters, which enable cell-to-cell communication, neuromodulators are released over large swathes of the brain, allowing them to exert more general effects.

"Neuromodulatory substances are thought to perfuse large areas of the brain and thereby alter the excitatory or inhibitory drive that neurons are receiving in a more point-to-point fashion," Sur says. "This suggests they must have very crucial brain-wide functions that are important for survival and for brain state regulation."

While scientists have learned much about the role of dopamine in motivation and reward pursuit, less is known about the other neuromodulators, including noradrenaline. It has been linked to arousal and boosting alertness, but too much noradrenaline can lead to anxiety.

Previous studies of the locus coeruleus, the brain's primary source of noradrenaline, have shown that it receives input from many parts of the brain and also sends its signals far and wide. In the new study, the MIT team set out to study its role in a specific type of learning called reinforcement learning, or learning by trial and error.

For this study, the researchers trained mice to push a lever when they heard a high-frequency tone, but not when they heard a low-frequency tone. When the mice responded correctly to the high-frequency tone, they received water, but if they pushed the lever when they heard a low-frequency tone, they received an unpleasant puff of air.

The mice also learned to push the lever harder when the tones were louder. When the volume was lower, they were more uncertain about whether they should push or not. And, when the researchers inhibited activity of the locus coeruleus, the mice became much more hesitant to push the lever when they heard low volume tones, suggesting that noradrenaline promotes taking a chance on getting a reward in situations where the payoff is uncertain.

"The animal is pushing because it wants a reward, and the locus coeruleus provides critical signals to say, push now, because the reward will come," Sur says.

The researchers also found that the neurons that generate this noradrenaline signal appear to send most of their output to the motor cortex, which offers more evidence that this signal stimulates the animals to take action.

Signaling surprise

While that initial burst of noradrenaline appears to stimulate the mice to take action, the researchers also found that a second burst often occurs after the trial is finished. When the mice received an expected reward, these bursts were small. However, when the outcome of the trial was a surprise, the bursts were much larger. For example, when a mouse received a puff of air instead of the reward it was expecting, the locus coeruleus sent out a large burst of noradrenaline.

In subsequent trials, that mouse would be much less likely to push the lever when it was uncertain it would receive a reward. "The animal is constantly adjusting its behavior," Sur says. "Even though it has already learned the task, it's adjusting its behavior based on what it has just done."

The mice also showed bursts of noradrenaline on trials when they received an unexpected reward. These bursts appeared to spread noradrenaline to many parts of the brain, including the prefrontal cortex, where planning and other higher cognitive functions occur.

"The surprise-encoding function of the locus coeruleus seem to be much more widespread in the brain, and that may make sense because everything we do is moderated by surprise," Sur says.

The researchers now plan to explore the possible synergy between noradrenaline and other neuromodulators, especially dopamine, which also responds to unexpected rewards. They also hope to learn more about how the prefrontal cortex stores the short-term memory of the input from the locus coeruleus to help the animals improve their performance in future trials.

More information: Mriganka Sur, Spatiotemporal dynamics of noradrenaline during learned behaviour, *Nature* (2022). DOI: 10.1038/s41586-022-04782-2. www.nature.com/articles/s41586-022-04782-2

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