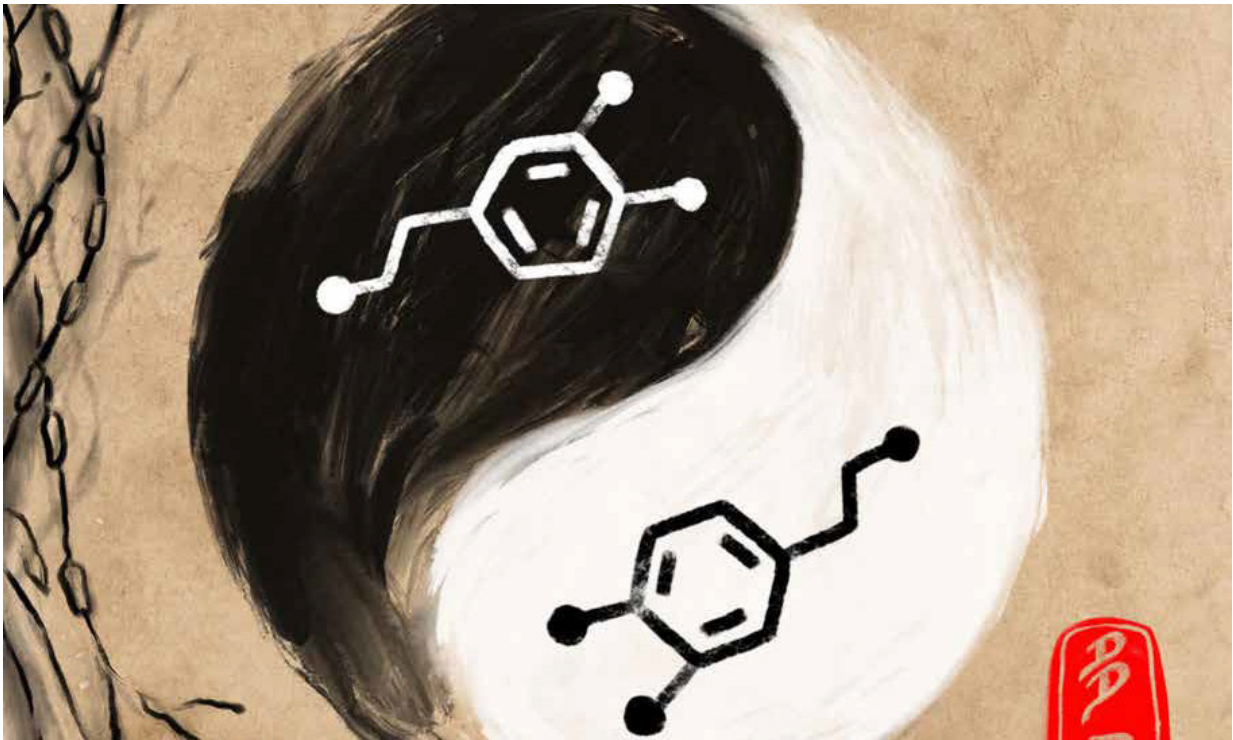


Dopamine's yin-yang personality: It's an upper and a downer

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UC Berkeley researchers have discovered that the brain neurotransmitter dopamine has a yin-yang personality, mediating both pleasure and pain. Credit: Christine Liu graphic

For decades, psychologists have viewed the neurotransmitter dopamine as a double-edged sword: released in the brain as a reward to train us to seek out pleasurable experiences, but also a "drug" the constant pursuit

of which leads to addiction.

According to a new study from the University of California, Berkeley, that's only one face of [dopamine](#). The flip side is that dopamine is also released in response to unpleasurable experiences, such as touching a hot tea kettle, presumably training the [brain](#) to avoid them in the future.

The yin-yang nature of dopamine could have implications for treatment of addiction and other mental disorders. In illnesses such as schizophrenia, for example, [dopamine levels](#) in different areas of the brain become abnormal, possibly because of an imbalance between the [reward](#) and avoidance circuits in the brain. Addiction, too, may result from an imbalance in reactions to pleasure and pain.

"In addiction, people only look for the next reward, and they will take a lot of risk to get the next shot of drugs of abuse," said Stephan Lammel, a UC Berkeley assistant professor of molecular and [cell biology](#) and the senior author of a paper describing the results in the journal *Neuron*.

"We currently do not know the neurobiological underpinnings of certain high-risk behaviors of individuals with addiction, such as sharing drug paraphernalia despite the proven risk of mortality and morbidity associated with it. An understanding of how drugs change neural circuits involved in aversion may have important implications for the persistent nature of drug-seeking behavior in the face of negative consequences."

Although some neuroscientists have long speculated about dopamine's potential role in the signaling of aversive events, its dual personality remained hidden until recently because the neurons in the brain that release dopamine in response to rewards are embedded in a different subcircuit than the neurons that release dopamine in response to aversive stimuli.

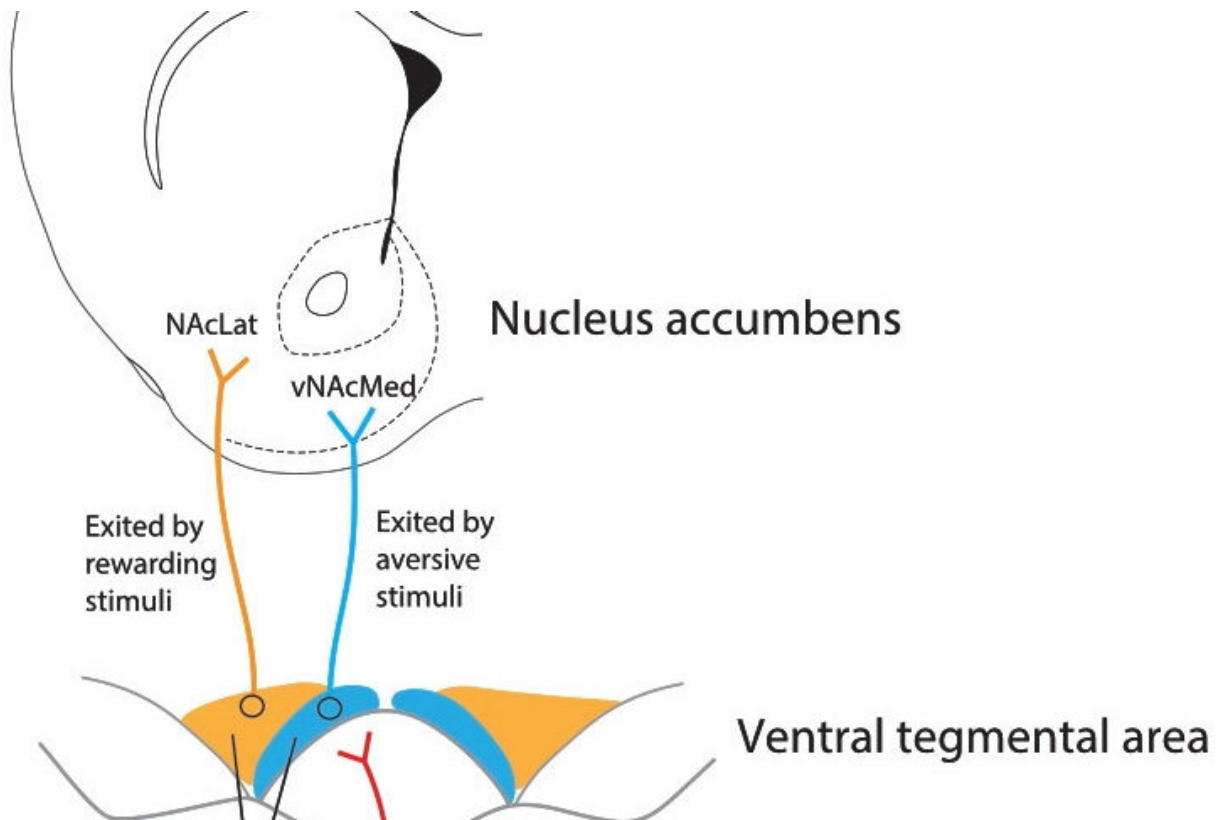
Johannes de Jong, the first author of the study, was able to

simultaneously record from both dopamine subcircuits by implanting fiber optic cannulas in two [brain regions](#)—separated by just a few millimeters—using a new technology called fiber photometry.

"Our work delineates for the first time the precise brain circuitry in which learning about rewarding and aversive outcomes occurs," Lammel said. "Having separate neuronal correlates for appetitive and aversive behavior in our brain may explain why we are striving for ever-greater rewards while simultaneously minimizing threats and dangers. Such balanced behavior of approach-and-avoidance learning is surely helpful for surviving competition in a constantly changing environment."

The newly discovered role for dopamine aligns with an increasing recognition that the neurotransmitter has quite different roles in different areas of the brain, exemplified by its function in voluntary movement, which is affected in Parkinson's disease. The results also explain earlier conflicting experiments, some of which showed that dopamine increases in response to aversive stimuli, while others did not.

"We have moved away from considering dopamine neurons as just a homogeneous cell population in the brain that mediates reward and pleasure to a more defined, nuanced picture of the role of dopamine, depending on where it is released in the brain," Lammel said.



Studies of the dopamine-producing area of the midbrain called the ventral tegmental area (center) have mostly focused on dopamine's role in reward. However, some evidence suggests that dopamine also plays a role in learning about aversive events, though the precise nature of the neural circuitry through which dopamine signals either reward or aversion is incompletely understood. In a new UC Berkeley study, researchers recorded from the axons of midbrain dopamine neurons that project to two areas of the nucleus accumbens (top) and discovered that there are two populations of neurons in the midbrain: the well-known circuit responding to positive motivational stimuli, but a parallel circuit responding to aversive events (blue). They also found that neurons from the lateral hypothalamus (bottom) were critical to priming aversion-sensing neurons to respond to painful stimuli. Credit: University of California - Berkeley

Reward prediction errors

Most of what is known about dopamine has been inferred from studies in rodents and monkeys, where researchers recorded from cells in a specific region of the brain that only contains reward-responsive dopamine neurons. It is possible, Lammel said, that through sampling biases, dopamine neurons that respond to aversive stimulation had been missed.

According to the reigning "reward prediction error hypothesis," dopamine neurons are activated and produce dopamine when an action is more rewarding than we expect, but they remain at baseline activity when the reward matches our expectations and show depressed activity when we receive less reward than predicted.

Dopamine changes neural circuits and trains the brain—for better or worse—to pursue the pleasurable and avoid the unpleasurable.

"Based on the reward prediction error hypothesis, the established tendency has been to emphasize dopamine involvement in reward, pleasure, addiction and reward-related learning, with less consideration of the involvement of dopamine in aversive processes," Lammel said.

To dissect the different dopamine subcircuits, de Jong and Lammel collaborated with the laboratory of Karl Deisseroth at Stanford University, who developed the fiber photometry technology a few years ago.

Fiber photometry involves threading thin, flexible fiber optic wires into the brain and recording fluorescent signals given off by neurons and their axons that release dopamine. The fluorescent markers are inserted into the neurons via a virus that targets only these cells.

In previous experiments in monkeys, Lammel said, scientists had recorded from dopamine cells without knowing where in the brain the

cells' axons reached, which could be areas millimeters from the cell body. Working with mice, de Jong recorded simultaneously from dopamine axons in the lateral and medial regions of an area called the nucleus accumbens, considered an integral part of the brain's reward circuits. He thus captured the activity of cells whose axons reach into these regions from the dopamine areas in the midbrain, specifically the ventral tegmental area.

To their surprise, axons in the medial area released dopamine in response to an aversive stimulus—a mild electrical shock to the foot—while those in the lateral area released dopamine only after positive stimuli.

"We have two different subtypes of dopamine cells: one population mediates attraction and one mediates aversion, and they are anatomically separated," Lammel said.

He hopes that these findings can be confirmed in monkeys and humans, and lead to new approaches to understanding and treating addiction and other brain maladies.

More information: Johannes W. de Jong et al, A Neural Circuit Mechanism for Encoding Aversive Stimuli in the Mesolimbic Dopamine System, *Neuron* (2018). [DOI: 10.1016/j.neuron.2018.11.005](https://doi.org/10.1016/j.neuron.2018.11.005)

Provided by University of California - Berkeley

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