**ESSAY**

**CELL AND MOLECULAR BIOLOGY**

**Trial and error**

Optogenetic techniques offer insight into the dopamine circuit underlying learning

*By Neir Eshel*

We are all prediction-making machines. Granted, our predictions are often wrong—as the old saying goes, “It’s tough to make predictions—especially about the future.” But even wrong predictions serve a purpose: They help us learn. Each time we make a choice, we predict the outcome of that choice. When the outcome matches our prediction, there is no need to learn. When the outcome is unexpected, however, we update our predictions, hoping to do better next time.

The idea that we learn by comparing predictions to reality has been a mainstay of animal learning theory since the 1950s (1–3) and is one of the foundations of machine learning (4). Remarkably, the brain has evolved a simple mechanism to make precisely these comparisons. In the 1990s, Wolfram Schultz and colleagues found that dopamine neurons in the midbrains of monkeys showed a curious response to reward (5). When the monkeys received an unexpected reward (in this case, a squirt of juice), dopamine neurons fired a burst of action potentials. When that same reward was expected, the neurons no longer fired. And if Schultz et al. played a trick on the monkeys, making them expect a reward but ultimately withholding that reward, the dopamine neurons dipped below their normal firing rate (6). Together, these results demonstrated that dopamine neurons signal prediction error, or the difference between actual and predicted value [see the figure (A)]. If an outcome is better than predicted, dopamine neurons fire; if an outcome is the same as predicted, there is no change in firing; and if an outcome is worse than predicted, dopamine neurons dip below baseline. The level of dopamine release then informs the rest of the brain when a prediction needs to be fixed and in what direction.

This basic finding—that dopamine neurons signal errors in reward prediction—revolutionized the study of learning in the brain by supplying a powerful, mechanistic model for how reinforcement affects behavior (7). Despite extensive study, however, little is known about how dopamine neurons actually calculate prediction error. What inputs do dopamine neurons combine and how do they combine them? To answer these questions, we merged molecular biology, electrophysiology, and computational analysis.

We focused on the ventral tegmental area (VTA), a small brainstem nucleus that produces dopamine. Although a majority of neurons in this region are dopamine neurons, a substantial minority use the inhibitory neurotransmitter γ-aminobutyric acid (GABA) instead. A recent study from our laboratory showed that these GABA neurons do not signal prediction error; rather, they encode reward expectation (8).

This finding raised a fascinating question: Could dopamine neurons use the GABA expectation signal to calculate prediction error? To find out, we used a virus to introduce the light-sensitive protein channelrhodopsin (ChR2) selectively in VTA GABA neurons. This enabled us to control the activity of VTA GABA neurons with light, a technique called optogenetics. We then implanted a set of electrodes surrounding a fiber optic cable into the VTA. Once the mice recovered from surgery, we recorded from the VTA and manipulated VTA GABA neuron activity, all while the mice performed simple learning tasks.

Optogenetics offers formidable precision, but there are potential pitfalls. In particular, it is easy to manipulate neural activity in ways that never occur in real life, producing results that are difficult to interpret. Our system avoided this pitfall, because we knew how VTA GABA neurons normally fire in our task. By recording during the manipulation, we made sure to mimic natural firing patterns.

When we stimulated VTA GABA neurons, dopamine neurons responded to unexpected rewards as if they were expected (9). Conversely, when we inhibited VTA GABA neurons, dopamine neurons responded to expected rewards as if they were unexpected. Finally, if we manipulated VTA GABA neurons simultaneously on both sides of the brain, we even changed the animals’ behavior. After training mice to expect a certain size of reward, we artificially increased the expectation level by stimulating VTA GABA neurons during...
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Neir Eshel is a psychiatry resident at Stanford University, pursuing a career at the interface of research and clinical practice. He is interested in how we learn about rewards and punishments, how we make decisions based on this knowledge, and how these systems break down in neuropsychiatric disease. He has conducted research at the National Institutes of Health, Princeton University, the World Health Organization, University College London, and Harvard University. Outside the laboratory and clinic, Neir plays clarinet in chamber groups and orchestras and is a passionate advocate for lesbian, gay, bisexual, and transgender (LGBT) health equality. www.sciencemag.org/content/354/6316/1108

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Originally from Germany, Sam Behjati read medicine at Oxford University and pursued postgraduate clinical training in London, UK. Funded by the Wellcome Trust, he joined the Cancer Genome Project of the Sanger Institute (UK) for doctoral research. Using a “mutational postcode” that cells acquire as they divide, Behjati has shown that it is feasible to reconstruct the early developmental process in the adult mouse. Building on ideas developed during his Ph.D. preparation, he now aims to define the embryonic origin and fate of childhood cancer cells. www.sciencemag.org/content/354/6316/1109.3

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REFERENCES AND NOTES


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