

PRIZE ESSAY



FINALIST
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Talia Lerner received her B.S. from Yale University and her Ph.D. from The University of California,

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NEUROBIOLOGY

The effortless custody of automatism

Differentially controlled dopamine signaling in the striatum may be critical to habit formation

By **Talia N. Lerner**

We rely on habits to get us through life. Grab your keys, back your car out of the driveway, navigate to work—each of these daily actions is made more fluid, and less error prone, with repetition and habit. As the father of modern psychology, William James (1), put it:

“The more of the details of our daily life we can hand over to the effortless custody of automatism, the more our higher powers of mind will be set free for their own proper work. There is no more miserable human being than one in whom nothing is habitual but indecision, and for whom the lighting of every cigar, the drinking of every cup, the time of rising and going to bed every day, and the beginning of every bit of work, are subjects of express volitional deliberation.”

But how do we transfer actions from express volitional control to automatism? Generally, a great deal of repetitive practice is required to perfect a new skill. Why? What about practice encourages the brain to consolidate a new action into an old habit?

DOPAMINE AND HABITUAL BEHAVIOR: WHAT'S THE CONNECTION?

Several major brain areas are implicated in the habit-formation process. Among the most prominent are the dorsal striatum and the midbrain dopamine system. As habits form, patterns of neural activity in the dorsal striatum shift. In the dorsomedial striatum, neural activity during the performance of a new task peaks in early acquisition and then fades as habits form, whereas in the dorsolateral striatum, activity emerges and solidifies over time, in sync with the habit's emergence (2). These habit-linked changes are likely caused by synaptic plasticity.

A large body of evidence points to the dopamine-dependent plasticity of cortical inputs onto striatal neurons as indispens-

able to habit formation (3–5), and my own graduate thesis focused on the molecular mechanisms by which dopamine acts as a master controller of the timing and direction of corticostriatal synaptic plasticity (6). The dopamine that controls striatal synaptic plasticity is supplied by the midbrain dopamine system. As a postdoc in the laboratory of Karl Deisseroth at Stanford University, I sought to examine the structure of the dopamine system as it relates to the control of habit formation. I hypothesized that dopamine circuits are structured to support the transfer of information between largely parallel corticostriatal systems, enabling the observed coordinated shifts in activity between striatal subregions. By understanding how dopamine signals to the dorsomedial and dorsolateral regions of the striatum might be differentially controlled, I could gain insight into the mechanisms by which habit formation circuitry is engaged to participate in action selection and how feedback from these habit circuits might then suppress volitional control.

DETERMINING DIFFERENTIAL CONTROL OF DOPAMINE SIGNALING

To begin, I used whole-brain circuit mapping and imaging techniques that were being developed at Stanford. Colleagues in Liqun Luo's lab were working on a rabies-mediated circuit-tracing strategy that allowed the mapping of whole-brain inputs to a cell type defined by its output. This technique, termed TRIO (7), was perfectly suited to determine whether dopamine signals to the dorsomedial and dorsolateral striatum could be generated by distinct combinations of inputs.

I combined TRIO mapping with a tissue-clearing method developed in the Deisseroth lab called CLARITY, which then enabled intact imaging of mapped dopamine circuits with light-sheet microscopy (8, 9). From these studies, I concluded that dopamine neurons did indeed receive differential inputs depending on their output targets. In particular, there was a bias toward reciprocal connectivity of striatal subregions with the dopamine neurons that project to those subregions (10).

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A SURPRISING OBSERVATION HINTS AT AN UNEXPECTED MECHANISM

To confirm my anatomical observations, I performed functional studies on the connection probabilities and synaptic strengths of striatal inputs to dopamine neurons using optogenetics and slice electrophysiology. This alternative method of circuit mapping broadly confirmed my TRIO findings, but to my surprise, it also led to the startling new observation that dorsolateral striatal inputs to dopamine neurons are substantially stronger than inputs from the dorsomedial striatum (10). This observation suggests a potential route for the suppression of dopamine transients to the dorsomedial striatum after heightened activity in the dorsolateral striatum as habits emerge.

AVERSIVE EVENTS PROVOKE DIFFERENT DOPAMINE RESPONSES

Finally, I addressed the question of whether dopamine carries information differently to the dorsomedial than to the dorsolateral striatum. Using fiber photometry, another new technique I helped develop in the Deisseroth lab, in which the activity of a genetically defined population of neu-

rons is recorded as a bulk fluorescence signal through a fiber optic brain implant, I tracked the activity of dopamine neurons during rewarding and aversive experiences. I compared the responses of dopamine neurons projecting to the dorsomedial striatum with those of dopamine neurons projecting to the dorsolateral striatum and found that aversive events, in particular, provoked profoundly different, indeed opposite, responses in the two populations (10).

In parallel experiments using and elaborating on the fiber photometry technology to include sampling signals from multiple brain regions simultaneously, my colleagues and I further showed that dopaminergic projections to additional output regions such as the prefrontal cortex can also carry distinct information (11). Together, these studies present a strong case for using circuit features to help define dopaminergic (and other) cell types in the brain (12).

UNRAVELING THE MYSTERY OF HABIT-FORMATION

Looking forward, I hypothesize that input-output-defined dopamine neurons are at the crux of the brain's habit engagement

circuitry. As animals learn and explore, the shift from volitional to habitual control of their actions will depend on cost-benefit calculations made by the circuits and synapses I have studied and will continue to study in my own lab. As we unravel the mysteries of habit formation across many levels of neurobiological investigation—from molecules to behavior—we will learn how to more efficiently slip new skills into the effortless custody of automatism while also developing strategies to wrench back conscious control of our more counterproductive habits from their sometimes defiant, iron grip. ■

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