Medical Xpress

Neural study explores how mice decide whether to eat or drink when they are both hungry and thirsty

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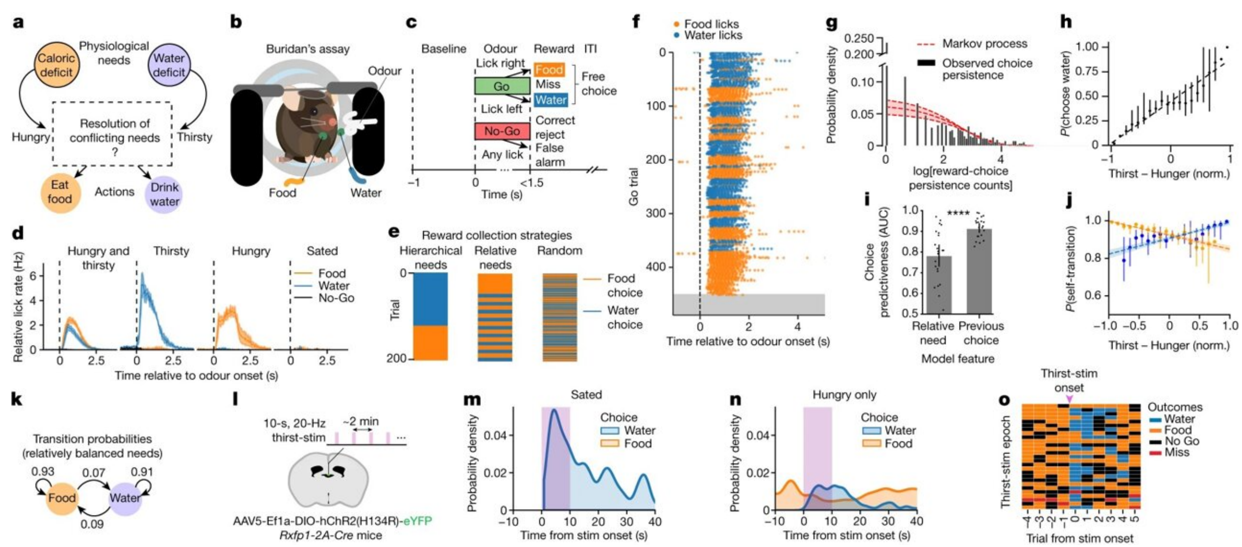

Reward choice under conflicting needs is structured by persistent behavioral states with stochastic transitions. **a**, The conceptual problem. **b**, Buridan's assay. A food- and water-restricted mouse is head-restrained with two equally accessible reward spouts, delivering salted liquid food and water, respectively. **c**, Trial structure. Go odor indicates reward availability and No-Go odor indicates reward unavailability after a variable inter-trial interval (ITI). After Go-odor onset, mice freely choose food or water reward by licking right or left, respectively. **d**, Licking behavior during Buridan's assay under different restriction conditions. The *y* axis shows average lick rate at a given spout, multiplied by the fraction of licks to that spout per session. Data are mean ± s.e.m. n = 15 mice, 22 sessions for food and water restriction; n = 3 mice, 3 sessions for water or food restriction only; n = 2 mice, 2 sessions for no restrictions. **e**, Hypothetical reward-choice patterns under different strategies. **f**, Behavioral session showing food and water licks across trials until satiation (gray). **g**, Reward-choice persistence counts distribution for all behavioral sessions with both food and water restriction. Dashed red line indicates probability density for log[persistence counts] generated by a sticky Markov process (geometric distribution fit to data, maximum likelihood shape parameter $P = 0.061$, 95% confidence interval [0.05, 0.074]). **h**, Probability of choosing a water reward on rewarded Go trials, fit by linear regression (dashed line) to observed relative need (normalized (norm.) thirst − hunger). $R^2 = 0.92$, slope = 0.426. Data are mean ± 95% confidence interval. The first and last two data points lack confidence intervals owing to too few data points. **i**, Prediction of current choice as a function of current needs or the most recent previous choice, based on a support vector machine model. AUC, receiver operating characteristic area under the curve. Data are mean ± 95% confidence interval. Two-sided paired *t*-test; $n = 22$ sessions, $t = -5.89$, $P = 6.28 \times 10^{-6}$. **j**, Self-transition probability fit by linear regression to normalized thirst − hunger. Data are mean ± 95% confidence interval. Water choice: $R^2 = 0.612$, slope = 0.07; food choice: $R^2 = 0.844$, slope = −0.077. **k**, Go-trial transition probability between reward choices. Probabilities are maximum likelihood estimates from trials with normalized thirst − hunger between −0.25 and 0.25. **g**–**k**, $n = 15$ mice, 22 sessions. **l**, Schematic of optogenetic activation of osmotic thirst ($RXFP1^+$) neurons in the subfornical organ (green) in 10-s epochs during Buridan's assay. **m**,**n**, Probability density (kernel density estimate) of food and water choices in Go trials as a function of optogenetic thirst stimulation (purple bars), in experiments on sated mice (**m**; $n = 2$ mice, 63 stim epochs) or on hungry-only mice (**n**; $n = 2$ mice, 69 stim epochs). **o**, Trial outcomes (color-coded, right) surrounding each optogenetic thirst-stimulation epoch (rows; $n = 27$) from a single session on a hungry-only mouse.

Making decisions is hard. Our choice often leaves something else on the table even when we know what we want. For a hungry mouse, every morsel counts. But what if the decision is more consequential than choosing between crumbs and cheese?

Stanford researchers investigated how mice resolve conflicts between basic needs in a study published in *Nature*. They presented mice that were both hungry and thirsty with equal access to food and water and watched to see what happened next.

The behavior of the mice surprised the scientists. Some gravitated first toward water, while others chose food. Then, with seemingly "random" periods of indulgence, they switched back and forth. In their study, Ph.D. candidate Ethan Richman, lead author of the paper, and colleagues in the departments of Biology, Psychiatry and Behavioral Sciences, and Bioengineering explored why.

This work builds on years of collaboration between co-senior authors Karl Deisseroth, the D.H. Chen Professor at Stanford Medicine, and Liqun Luo, the Ann and Bill Swindells Professor in the School of Humanities and Sciences, to understand how the brain keeps the body alive.

Buridan's what?

"There's this old philosophical quandary called Buridan's Ass," explained Richman, "where you have a donkey that is equally hungry and thirsty and equally far from food and water." The concept was posited by philosophers Aristotle, Jean Buridan, and Baruch Spinoza, in different forms. The question was whether the donkey would choose one need over the other or remain stubbornly in the middle.

But animals are constantly making choices. We must satisfy our needs to maintain homeostasis. Richman and colleagues wanted to know how the brain directs traffic through conflicting signals to flout Buridan. They call their behavioral experiment "Buridan's Assay."

If hunger or thirst directly motivated a mouse to eat or drink, it would switch as soon as one need outweighed the other. When needs were equal, the mouse would be stuck. This is not what the researchers observed. "Our data indicate that thirst and hunger don't act as direct forces on behavior," said Richman. "Instead, they modulate behavior more indirectly. They're influencing what we think of as the current goal of the mouse."

A mouse's goal

We often think of choices as a decisive moment. The researchers wanted to understand when and where choices between food and water originate in the brain. Using recent advances in recording technology, they monitored activity from individual neurons spread across the mouse brain.

To their surprise, neuron activity patterns throughout the brain predicted the mouse's choice, even before it was presented with options. "Instead of a single moment of choice, the mouse's brain is constantly broadcasting its current goal," said Richman.

"Outcomes of the hardest choices you make—when options are closely balanced in importance, but the categories are fundamentally different—may have to do with the state your brain happened to be in, even before the choice was presented," said Deisseroth. "That's an interesting outcome and it helps us understand aspects of human behavior better."

Exploring the random

The researchers found that hungry and thirsty mice often make the same choice repeatedly before suddenly switching. "In eating mode, the mouse will just eat and eat. In drinking mode, it will drink and drink," said Luo.

"But there is an aspect of randomness that causes them to switch between these two. That way, in the long run, they fulfill both needs, even if at any given time they are only choosing one."

To test this apparent randomness, the researchers ran another experiment, this time with hungry mice. As the mice ate, scientists introduced thirst through a technique called optogenetics. With optogenetics, they used light to activate neurons causing thirst. Sometimes, the mice switched to water, and sometimes, they ignored it and kept eating. The level of thirst was the same each time, leading the researchers to conclude there is a key randomness influencing the mouse's goal.

The scientists were perplexed by the interplay between this randomness and the relative intensities of hunger and thirst. To better understand it, they turned to mathematical modeling. Inspired by a conceptual resemblance between their results and a distant field of physics, the researchers borrowed, tweaked, and simulated several equations.

"We were extremely surprised and excited to find that a few simple equations from a seemingly unrelated discipline could closely predict aspects of mouse behavior and brain activity," said Richman. The results of their modeling suggested that the brain activity relating to the mouse's goal is constantly in motion. It gets trapped by needs like hunger and thirst. To escape and transition from one goal to another, the mouse relies on a lucky series of random activity.

This work establishes the importance of the brain's shifting baseline state when it comes to decision-making. In the future, the researchers will explore what sets the tone and why decisions don't always make sense.

Beyond Buridan

"In terms of Buridan's Ass, we can say that the donkey's mind is made up before it is given a choice," says Richman, "and if it has to wait, then its choice may spontaneously switch." Clinical applications for this work in the human context are a bit more complex. "As a psychiatrist, I often think about how we make healthy (adaptive) or harmful (maladaptive) decisions," said Deisseroth. (Maladaptive behaviors impact people's ability to make decisions in their best interest and they are common in psychiatric disorders.)

"It's very hard for family and friends to see loved ones act against their own survival drives. It may help to understand the choices made as reflecting the underlying dynamical landscape of the patient's brain, affected by the disorder more than by the patient's conscious volition."

Although this work might not explain human behavior, it begins to reveal an important framework for decision-making. "This is basic discovery science that depends on pretty advanced neuro-engineering, but at the core, we address universal questions that people think about and experience all the time," said Deisseroth. "It's exciting to develop and apply modern tools to address these very old, deep, and personal questions."

More information: Richman, E.B. et al. Neural landscape diffusion resolves conflicts between needs across time, *Nature* (2023). DOI: 10.1038/s41586-023-06715-z. www.nature.com/articles/s41586-023-06715-z

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