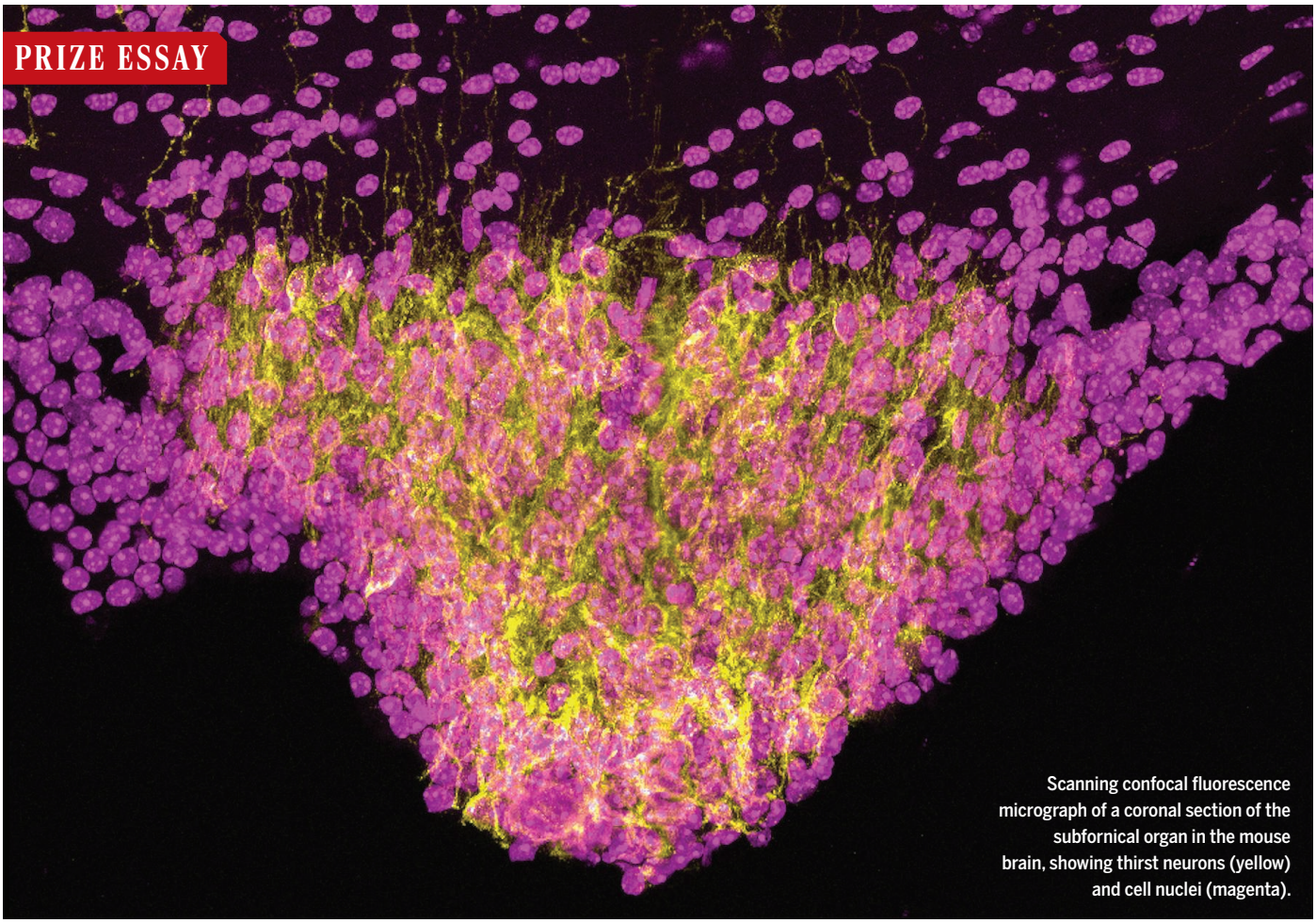
PRIZE ESSAY



Scanning confocal fluorescence micrograph of a coronal section of the subfornical organ in the mouse brain, showing thirst neurons (yellow) and cell nuclei (magenta).

PHOTO: CHRISTOPHER ZIMMERMAN

NEUROBIOLOGY

The origins of thirst

Sensory signals arise throughout the body and converge in the brain to regulate drinking

By **Christopher A. Zimmerman**

We experience thirst every day, but where does this sensation come from? In the 1950s, Bengt Andersson proposed a tantalizing answer: Our brains might contain an "osmosensor" (*1*) that governs thirst, which consists of a group of cells that sense when we are dehydrated by directly monitoring the osmolarity of the blood. In a series of pioneering experiments, Andersson systematically infused salt into the brains of goats in an attempt to locate this osmosensor (*2*, *3*). He ultimately discovered a small area within the hypothalamus where even minute amounts of salt triggered immediate, voracious drinking. Subsequent studies established that Andersson's osmosensor encompasses the subfornical organ (SFO), a brain region that is distinctively suited to detecting blood osmolarity because it lies outside the blood-brain barrier (*4*).

The osmosensor model is powerful because it explains how dehydration generates thirst, but it has a crucial shortcoming: Drinking behavior is regulated on a fast, moment-by-moment basis that cannot be explained by slow changes in blood osmolarity. Consider that drinking immediately satiates thirst, even though the water imbibed is not absorbed for many minutes (*5*, *6*), and that eating stimulates prandial drinking long before the ingested food enters the bloodstream (*7*, *8*). How does the brain bridge these disparate time scales to dynamically adjust our sense of thirst?

I reasoned that we might gain new insight into this longstanding question by recording the activity of thirst-promoting neurons in living animals. My colleagues and I thus began by genetically labeling the SFO neurons that comprise Andersson's osmosensor and confirming that these cells are essential for dehydration-induced drinking (*9*). We then set out to observe the neural dynamics underlying thirst in behaving mice (*10*, *11*).

THIRST NEURONS ARE MORE THAN SIMPLE DEHYDRATION SENSORS

If SFO neurons are genuine osmosensors, then we would expect them to simply encode an animal's dehydration level. Consistent with this idea, our initial fiber photometry recordings demonstrated that these neurons are dose-dependently activated by increases in blood osmolarity (*10*).

It was therefore surprising to discover that SFO neurons are also rapidly regulated

Princeton Neuroscience Institute, Princeton University, Princeton, NJ, USA.
Email: czimmerman@princeton.edu

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during eating and drinking, well in advance of any impact food and drink might have on the blood (*10*). For example, their activity decreases every time a mouse licks from a water bottle and increases with every bite of food. This counterintuitive finding indicated that SFO neurons—long viewed as merely passive sensors of dehydration—must receive a second class of signals that operate on the fast time scale of behavior.

LAYERS OF SIGNALS ARISE FROM THE DIGESTIVE TRACT DURING INGESTION

To pinpoint the origin of these signals, we traced the flow of water through the digestive tract of the mouse. We found that fluid detection in the mouth triggers a near-instantaneous inhibitory signal that closely tracks the volume ingested (*10*). Temperature sensing contributes to this process—SFO neurons are most efficiently inhibited by drinking cold water, a phenomenon that could be reproduced through isolated oral cooling. This may explain why we experience cold drinks as especially thirst-quenching and pleasurable (*12*, *13*).

Using an intragastric infusion paradigm, we next discovered that the osmolarity of ingested fluids is precisely measured in the gastrointestinal tract and then rapidly transmitted to the brain by the vagus nerve (*11*). This gut-to-brain osmolarity signal sustains the inhibition of SFO neurons produced by oral volume signals and satiates thirst if pure water is drunk. By contrast, detection of hypertonic fluids in the gut causes SFO activity to rebound to the "thirsty" state. Thus, drinking generates layers of signals that enable thirst neurons to predict how ingested fluids will affect hydration in the future and then adjust drinking preemptively. This simple model explains how drinking can rapidly quench thirst yet also be properly calibrated to match an animal's level of dehydration (*5*, *6*).

Does the body notify the thirst system about other behaviors that affect hydration? We found that eating triggers additional signals that activate SFO neurons in anticipation of food absorption (*10*). This activation drives prandial drinking or, if water is unavailable, suppresses further feeding. This suggests a neural basis for the widespread coordination of eating and drinking (*7*, *8*).

To test the causal role of the body-to-brain signals identified by our recording experiments, we used optogenetics to precisely manipulate each of them during behavior. This allowed us to confirm that these signals are necessary for thirst satiation, prandial thirst, and dehydration-induced anorexia (*10*, *11*), and thus account for most normal drinking behavior.

GRAND PRIZE WINNER

Christopher Zimmerman

Christopher Zimmerman received his undergraduate degrees from the University of Pittsburgh and a Ph.D. from the University of California, San Francisco. His thesis research focused on the neural mechanisms that govern thirst and drinking behavior. Zimmerman is currently a postdoctoral fellow at the Princeton Neuroscience Institute, where he continues to study the neural processes underlying motivated behaviors.

FINALIST

Tara LeGates

Tara LeGates received her B.S. in Biopsychology from Rider University and a Ph.D. from Johns Hopkins University. She completed a postdoctoral fellowship at the University of Maryland School of Medicine, where she established the importance of the strength and plasticity of hippocampus-nucleus accumbens synapses and reward behavior. LeGates is now an assistant professor at the University of Maryland, Baltimore County (UMBC). Her lab studies how neuronal circuits integrate information to regulate behavior and their alterations in psychiatric disorders. **www.sciencemag.org/content/370/6512/46.1**

FINALIST

Riccardo Beltramo

Riccardo Beltramo received his undergraduate degree from the University of Turin and a Ph.D. from the Italian Institute of Technology. After his doctoral training, Beltramo joined the Howard Hughes Medical Institute at the University of California, San Diego and the University of California, San Francisco, where he is completing his postdoctoral work. He studies sensory perception in the mouse visual system, focusing on understanding how cortical and subcortical neural circuits process visual information to drive behavior. **www.sciencemag.org/content/370/6512/46.2**

SIGNALS CONVERGE ONTO INDIVIDUAL NEURONS TO DYNAMICALLY ADJUST THIRST

The discovery of diverse inputs to SFO neurons raises the fundamental question of how signals are processed by the individual cells that comprise the thirst system. Do they flow in segregated "streams" or do they interact? To answer this question, we used microendoscopic imaging to track the activity of single neurons during dehydration, drinking, and intragastric infusion (*11*). This revealed a simple processing logic: The signals arising from the mouth, gut, and blood converge onto the same individual thirst neurons, thereby enabling every cell to continuously integrate information about current hydration status with the predicted consequences of ongoing ingestion.

In a parallel series of experiments, we showed that downstream brain regions use this integrated representation to coordinate the various components of the body's response to dehydration, including not only drinking but also cardiovascular adjustments, hormone secretion, and changes to emotional valence (*11*, *14*).

CONCLUSIONS

Thirst is governed by a sensory system, analogous to vision or hearing. Unlike these exterosensory systems, however, the neural dynamics underlying thirst were previously unknown. Our recordings revealed that thirst is regulated by layers of signals that arise throughout the body and converge onto individual neurons in the forebrain. This convergence occurs at the first node in the thirst system—the SFO—and generates a real-time estimate of the body's need for water that downstream nodes use to dynamically adjust drinking, valence, and cardiovascular physiology (*10*, *11*, *14*). Our findings reveal fundamental principles that govern ingestive behavior (*15*, *16*) and provide neural mechanisms that can potentially explain long-enigmatic elements of everyday human experience, including the speed of thirst satiation, the prevalence of drinking during meals, and the thirst-quenching power of oral cooling. ■

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