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# When memory shapes appetite: A top-down peptidergic gate for context-dependent feeding

Tianbo Qi[1,2] and Li Ye[1,2,*]
[1]Department of Neuroscience, Dorris Neuroscience Center, Scripps Research, San Diego, CA, USA
[2]Howard Hughes Medical Institute, Chevy Chase, MD, USA
*Correspondence: liye@scripps.edu
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**In this issue of *Neuron*, Goode et al.[1] identify a hippocampus-septum-hypothalamus circuit in which prodynorphin-expressing septal neurons regulate contextual feeding. By transmitting aversive contextual signals, this pathway gates food consumption according to learned environmental context.**

We eat not only because we are hungry. Sometimes we eat because the environment we are in reminds us of eating—the kitchen where snacks appear, the café that signals pastries—or, conversely, we may lose our appetite in an alley that feels unsafe. These everyday experiences highlight how feeding behavior is shaped not only by internal metabolic need but also by learned associations with environmental context. This raises a key question: how do neural circuits that encode context and past experience interact with hypothalamic feeding networks?

The hippocampus has long been recognized as a key structure for encoding contextual and spatial memories. Neurons in the dorsal hippocampus (DHPC) form ensembles that represent specific environments,[2] allowing animals to distinguish between places associated with reward, danger, or other experiences. These hippocampal representations provide a framework for linking experiences with particular contexts, enabling animals to anticipate outcomes based on where they are. Consistent with this role, accumulating evidence suggests that hippocampal activity can influence motivated and homeostatic behaviors, including feeding, by integrating memory with current behavioral demands.[3]

Anatomically, the hippocampus is well positioned to exert top-down influence over hypothalamic circuits through intermediate structures such as the lateral septum.[4] The lateral area of the hypothalamus (LHA) serves as a key node in the neural control of feeding, integrating metabolic signals with sensory and cognitive inputs.[5] By transmitting contextual information from the hippocampus to hypothalamic feeding centers, the hippocampal-septal pathway may allow environmental experience to calibrate feeding decisions, ensuring that food consumption is not driven solely by internal energy state but is adapted to the surrounding environment.

In the current issue of *Neuron*, Goode et al. delineate a DHPC → dorsolateral septum (DLS) (prodynorphin+) → LHA pathway that gates feeding (and defensive freezing) according to learned context. The authors started with a genetic-anatomical characterization of the somatostatin (Sst) neurons in the lateral septum, a population previously established to encode context-specific behaviors.[6] They found a distinct subpopulation in the DLS expressing the neuropeptide prodynorphin (Pdyn). These neurons receive inputs from the DHPC, a key region for context processing, and project to a canonical feeding center in the LHA, establishing DLS Pdyn cells as a compelling candidate for relaying contextual information from the hippocampus to hypothalamic feeding circuits.

Goode et al. next asked whether these neurons indeed functionally contribute to context-dependent feeding behavior. Through circuit manipulation, they found that activation of these neurons suppressed feeding and promoted defensive freezing, whereas inhibition disrupted the contextual modulation of feeding. Notably, this effect depends on the DHPC input, indicating that contextual information from the hippocampus is necessary for the effect. These findings support the idea that the DHPC-DLS-LHA pathway integrates learned context to gate food intake.

Perhaps the most intriguing part of the story is that the septal node is prodynorphinergic. Pdyn is the precursor for dynorphin, an opioid neuropeptide that acts primarily through kappa opioid receptors (KORs) and is often associated with aversion, stress, and negative reinforcement.[7] Goode et al. show that loss of function of Pdyn-KOR signaling phenocopies circuit silencing, suggesting that dynorphin is not merely a molecular marker but an essential functional component—dynorphin signaling within this circuit is required for integrating contextual information into feeding decisions. In this framework, dynorphin release may modulate hypothalamic circuit dynamics to encode the motivational significance of different environments. More broadly, the involvement of dynorphin links contextual control of feeding to neuromodulatory systems traditionally associated with stress and negative affect.

How does this circuit operate endogenously? To answer this question, Goode et al. recorded the activity of DLS Pdyn neurons and found that they exhibit learned context-dependent activity patterns: eating in familiar, food-associated contexts is accompanied by a larger decrease in activity, lifting the inhibitory gate and permitting greater food intake.

This activity pattern further supports the idea that these neurons act as a context-dependent gate, dynamically constraining food intake according to the surrounding environment.

The discovery of the DHPC-DLS-LHA pathway highlights how memory circuits interact with hypothalamic systems to shape behavior. While hypothalamic feeding networks respond to metabolic signals such as hormones and nutrient status, hippocampal circuits encode the history and meaning of specific environments. By routing contextual information to the LHA, the brain can dynamically adjust feeding behavior based on past experience. Such a mechanism ensures that animals do not simply eat whenever energy demand arises but that they instead incorporate contextual knowledge about safety, reward availability, and environmental conditions.

This circuit also illustrates a broader principle: homeostatic and cognitive networks are deeply intertwined. Feeding decisions emerge from interactions among metabolic signals, reward processing, and memory systems. The lateral septum, long recognized as a relay between the hippocampus and hypothalamus, appears to play a key role in this integration by transforming contextual information into homeostatic control signals. Consistent with this idea, recent work has shown that hippocampus-septum activity can influence peripheral glucose regulation, suggesting that hippocampal memory circuits can also interact directly with the hypothalamic metabolic control systems.[8]

There are, however, several outstanding questions that follow directly from this work. First, how exactly do hippocampal ensembles representing specific contexts drive activity in DLS Pdyn neurons? Future work combining large-scale hippocampal recordings with circuit tracing may reveal the precise hippocampal neural codes that are transmitted along this pathway. Second, how does this DHPC-DLS circuit relate to other hippocampus-septum pathways that have been implicated in contextual feeding? For example, dentate gyrus Drd2 neurons project to the septum and have been shown to regulate similar behavior.[9] Finally, given the involvement of dynorphin and KOR signaling, it will be important to determine whether this circuit contributes to pathological feeding behaviors in humans, such as stress-induced overeating or binge eating triggered by environmental cues.[10]

Altogether, the work by Goode et al. provides an important step toward understanding how the brain integrates cognitive and homeostatic signals to guide adaptive behavior. By identifying a hippocampus-septum-hypothalamus circuit that links contextual representations to feeding control, the study bridges cognitive memory systems with ancient homeostatic networks. Such integration likely allows animals to flexibly adjust feeding decisions in complex and changing environments. As neural circuits underlying feeding continue to be dissected, understanding how cognitive information interacts with metabolic control systems may offer new insights into both adaptive behavior and the neural basis of eating disorders.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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