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Neuroscience: Tantalized Flies Are Primed for Satiety

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How animals maintain and switch between distinct motivational states is an important question in neuroscience. New work in *Drosophila* identifies an excitatory neuronal circuit that builds up mating drive while priming itself for satiety.

Tantalus stands chin deep in a pool of water, beneath the shade of fruit trees, their near branches heavy with figs, olives and pomegranates [1]. Parched, he tucks his chin for a sip, only for the water to magically recede. The fruit branches above him, too, swing just beyond his reach. There he remains, eternally driven to drink and eat, and eternally unable to satisfy his needs. The story of Tantalus highlights how internal drives, such as hunger and thirst, motivate behaviors, such as searching for food and water.

But hidden in this story is our implicit knowledge of what would happen if Tantalus were to ever eat or drink: consuming the water or fruit would quench his hunger and thirst, leading to a dramatic change in his behavior, but only temporarily, until the desire for food and water rises again. This cycle exists in nearly all animals — an increasing motivational drive, actions to fulfill a need, achievement of satiety, and resumption of desire. How does this cycle of motivation and satiety play out in the brain, and are the two, as Tantalus' story suggests, intimately intertwined? A recent study in *Current Biology* by Stephen Zhang, Dragana Rogulja and Michael Crickmore [2] addresses this question in *Drosophila melanogaster* and uncovers a recurrent network that increases and maintains motivational drive while simultaneously priming itself for satiety.

Male *Drosophila* are motivated not only to eat and drink, but also to mate [3]. Abstinence elevates mating drive such that a virgin male fly, within mere seconds of finding a female fly, will perform a series of courtship actions, including production of an elaborate song oriented towards his potential mate [4]. This drive persists, leading him to copulate with several female flies if given the opportunity; but successive copulations eventually lower the desire to court again [5]. Mating drive plays a key role in activating P1 neurons, which integrate sensory cues from conspecific females to drive various courtship actions [6–9]. A previous study from this group [5] showed that the activity of P1 neurons is modulated by a local dopamine signal that represents the male fly's current mating drive. Abstinence increases dopamine signaling and sensitizes P1 to female cues; satiety, on the other hand, decreases dopamine signaling and stunts P1 responses [5,10]. In their new study [2], Zhang and colleagues tackle three outstanding questions: what increases and sustains mating drive, what diminishes it, and what regulates its eventual recovery after satiety?

Absence makes the heart grow fonder— for flies, abstinence from mating makes for tantalized males that maintain a high mating drive for days. Zhang and colleagues [2] show that mating drive builds up and persists as a result of an excitatory neural loop comprising at least two clusters of neurons: about four pCd and about seven neuropeptide F (NPF) neurons. Persistent neural activity can reverberate through such excitatory loops and is known to store memories and maintain behavioral states [11–14]. Zhang and colleagues [2] show that neural activity in the pCd–NPF loop is positively reflected in downstream dopamine neurons that modulate courtship drive, linking their new findings with known courtship-circuit modules (Figure 1A). However, these findings will need to be reconciled with studies that suggest that inhibition of NPF neurons increases mating behaviors [15].

How do successive copulations diminish mating drive? Zhang and colleagues [2] identify a set of about 25 neurons, with dendrites projecting into the genitalia and with axons reaching the brain, that report copulation status. Activating these 'copulation reporting neurons' directly inhibits NPF neurons, which contributes to a net drop in the neural activity of the pCd–NPF loop (Figure 1A). In support of this mechanism, experimentally inhibiting copulation-reporting neurons makes male flies insatiable, as if they are unable to sense that they have mated. Typically, male flies take a few days to recover their mating drive after satiety. This delay is likely to be important for synchronizing the display of mating behaviors with the production of sperm and seminal fluids. What explains the recovery of mating drive after copulation? Zhang and colleagues [2] discover that the pCd–NPF loop, remarkably, is self-primed for satiety — activity in the loop leads to the accumulation of a molecule that acts to curtail the loop's own re-excitation. The authors find that activity of the transcription factor CREB2 increases with neural activity in the pCd–NPF loop in abstinent males. CREB2 activity reshapes the molecular profiles of pCd and NPF neurons to restrain the buildup of neural activity in the loop, including increasing the expression of a potassium leak channel, Task7, in pCd neurons (Figure 1B). This is reminiscent of how changes in sleep pressure are reflected in the molecular landscape of sleep-control neurons: the activity of sleep-promoting neurons is tightly

regulated by distinct potassium conductances that change with sleep need, and these conductances in turn alter the firing properties of neurons to drive waking or sleeping [16]. Similarly, when mating drive is high, CREB2 activity increases to prepare the loop for future inhibition, thus modulating mating drive with sexual experience. These results are striking because they link circuit and molecular mechanisms directly to an ethologically relevant behavior. They inspire a suite of questions about how persistent activity is generated and maintained within the pCd–NPF loop, particularly over timescales that are relevant for behavior.

While the new study by Zhang and colleagues [2] has resolved several key questions about the balance between motivation and satiety during courtship, some questions remain. For one, animals may experience multiple motivational drives, sometimes simultaneously (e.g. hunger and thirst), and these drives may elicit distinct behaviors. Are the neural substrates and computations that control motivation generalizable or unique to each motivational drive? Another recent study, in support of the recurrent network model proposed by Zhang and colleagues [2], showed that persistent activity in pCd neurons is required to sustain not only courtship but also aggressive behaviors [14]. pCd neurons are functionally downstream of P1 and are required for behavioral persistence, suggesting that there may be multiple recurrent networks regulating drives for multiple sexual and social behaviors. Another question is how long timescale motivational drives interact with the precise control of behavioral actions during courtship? Male courtship song is dynamically patterned both by sensory feedback from the female fly and by fast-switching internal states, on timescales of milliseconds to seconds [4,17] — does the pCd–NPF loop modulate activity in sensorimotor circuits that dynamically pattern singing and other courtship behaviors? Resolving these mechanisms will depend on mapping the detailed connectivity of such networks of neurons at synaptic resolution [18], following methods developed in other studies to link neural connectivity and the logic underlying olfactory processing and learning [19,20].

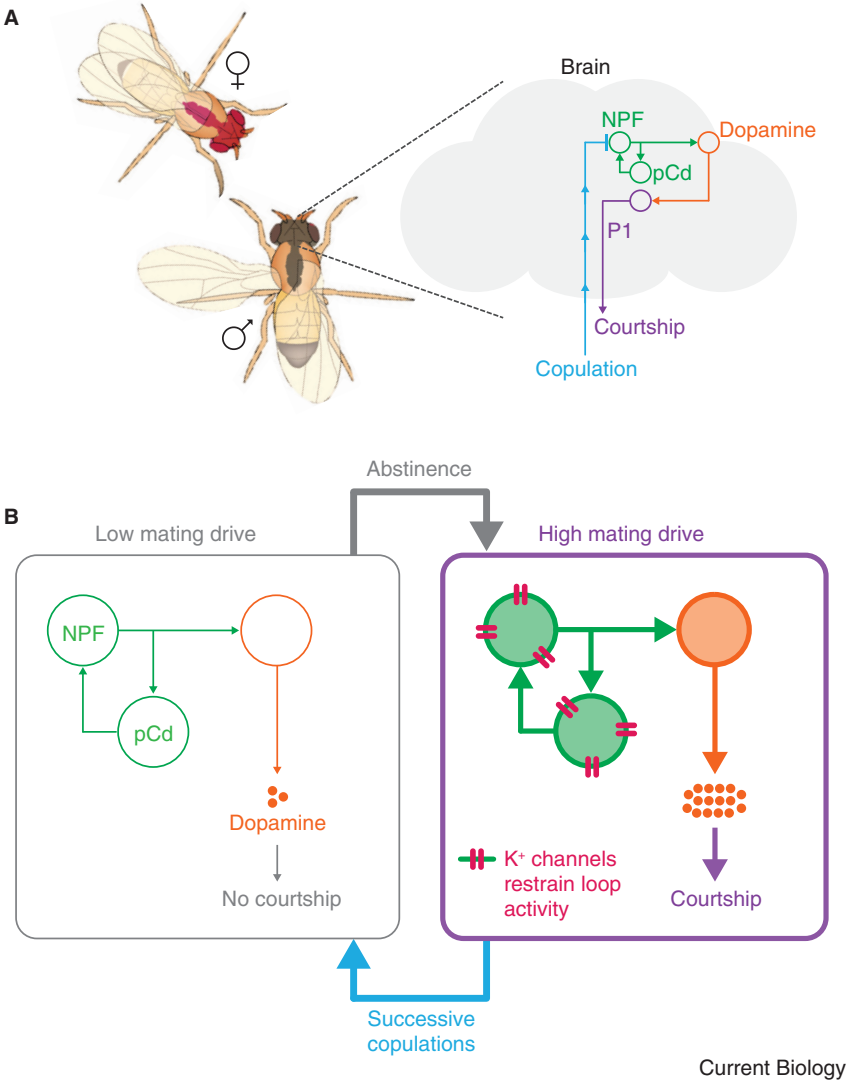

Figure 1. Neural circuit control of mating drive.
(A) Motivated male fruit flies court female flies by generating a courtship song via wing vibration. The courtship circuit includes the NPF–pCd excitatory loop described by Zhang and colleagues [2], which activates dopamine neurons that modulate the activity of P1 courtship-promoting neurons. Copulation reporting neurons (blue) inhibit NPF neurons, thereby decreasing mating drive. (B) Activity in the NPF–pCd loop reflects mating drive. Successive copulations decrease activity in the NPF–pCd loop, which is reflected in downstream dopamine neurons (left). Mating drive increases with abstinence as activity in the pCd-NPF loop ramps, but simultaneously, a molecular program builds up to restrain electrical activity and prime the circuit for inhibition (right).

Altogether, Zhang and colleagues [2] propose a neural circuit model to explain the ebb and flow of motivation: a recurrent excitatory loop increases and sustains motivational drive, and a molecular program primes this loop for future inhibition — a tantalizing model for probing the internal and external expressions of motivation. Indeed, self-regulating networks may be a general feature of nervous systems balancing the push and pull of motivational drives in order to ensure appropriate behaviors are executed, when the need arises.

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