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Behavioral neuroscience: Flexible integration on the fly

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Integrating noisy stimuli over time is crucial to making appropriate decisions. New studies in *Drosophila* revealed that threat responses can be flexibly modulated during courtship and mating. Towards the end of mating, flies adaptively prolong their threat integration time window.

The world is inherently noisy, with countless things happening at once. Imagine yourself walking down a New York street that pulses with energy. Towering buildings and flashing signs surround busy crowds. Horns blare, conversations overlap, and food carts fill the air with rich aromas. Bright yellow taxis, city buses, and cars clog the streets. Upon deciding to cross the street, however, you should focus on traffic and ignore the food smell and chatter.

Our decisions can be influenced by other humans, animals, and objects that engage all our senses simultaneously: vision, smell, hearing, taste, and touch. How do we know what to pay attention to and also *when* we should pay attention to what? We are unaware of many things happening around us, as our brain cannot constantly integrate all available information. It needs to flexibly filter out what is most important to us at every single moment, which can change. At lunchtime, we will focus on the food cart smell, which will help us satisfy our needs and find hidden delicacies. However, it may also lead us to overlook the dangerous vehicles. Shifting priorities is usually a trade-off and, quite often, it is necessary to expose ourselves to dangers and take risks to successfully adapt to changes in our environment or internal states.

In the fruit fly, *Drosophila melanogaster*, mating is the ecologically most critical behavior as this is how genes are passed on in the cycle of life. Mating, however, is also costly as flies are distracted for a long time and exposed to threats. Thus, flies should invest enough time to mate successfully, but not too much, as their survival and additional mating opportunities will allow for more offspring. This complex behavioral trade-off is an excellent model for studying the mechanisms underlying temporal integration of sensory information and flexible decision-making. This trade-off requires accurate timekeeping of mating duration and sensory integration from multiple stimuli and modalities.

A new study from Cazalé-Debat, Scheunemann, Rezaval and colleagues, published in a recent issue of *Nature*, investigated decision-making during courtship, the earliest mating phase[1]. Flies perform an intricate courtship ritual with the male tapping and singing to seduce the female. Eventually, the male will try to bend his abdomen to initiate the copulation. Male flies respond differently to visual threats during courtship phases. They are likely to stop courtship when they have invested little time, but being close to successful mating, they ignore a potentially dangerous threat (Figure 1).

Another new study from Gautham, Crickmore and colleagues, also published in *Nature*, investigated threat perception during copulation[2]. Usually, the longer the flies mate, the more successful is the mating. The whole process can last up to 20 minutes. Sperm transfer already takes place after six minutes but, as long as the male is engaged with the female, no other competitors can mate with her. During the first six minutes, flies almost completely stop responding to threats and rewards[3]. Crickmore and colleagues now show that flies slowly start responding to heat threats and wind gusts towards the end of the 20-minute copulation[2]. Ten minutes after copulation onset, few couples terminate mating, and when exposed to repeating threat pulses, the number of couples responding per pulse does not increase. Fifteen minutes into copulation, however, flies respond more strongly to later repeating pulses than to the first threat, indicating that they can now accumulate threat information over a longer time (Figure 1). The higher the level of certainty about the success of mating, the more likely they get distracted by a threat and terminate mating. Flies are not more sensitive to weak threat stimuli, but they become more attentive to consecutive events due to the prolongation of the time window during which threat stimuli are integrated.

How and where are these changes in threat response implemented in the brain? Both studies show that dopamine is involved in motivational change toward mating (Figure 1). Dopamine, a brain-wide neurotransmitter, is known to report prediction errors, and to mediate reward and punishment signals during learning[4], but it has also been implicated in the integration of multisensory cues, and internal states, such as persistence[5,6]. The two new studies in *Drosophila* now show that dopamine levels record the succession of mating and underlie different neural modulations[1,2]. During courtship, dopamine neuron activity ramps up in the brain as flies integrate how often they attempt copulation by bending their abdomen. Whether this integration happens in the dopamine neurons remains unclear. The released dopamine inhibits threat detector neurons in the visual system via Dop2R receptor activation. The more dopamine, the more 'blind' the flies are to a threat[1] (Figure 1).This is in line with previous data from the Crickmore lab, which showed that dopamine modulates the mating-promoting P1 neuron via Dop2R receptors that is necessary for normal courtship behavior[7].

During copulation, dopamine levels are high and decrease slowly over many minutes. Crickmore and colleagues now show that during this final mating phase, dopamine acts as an enhancer for CAMKII, an enzyme that degrades cAMP

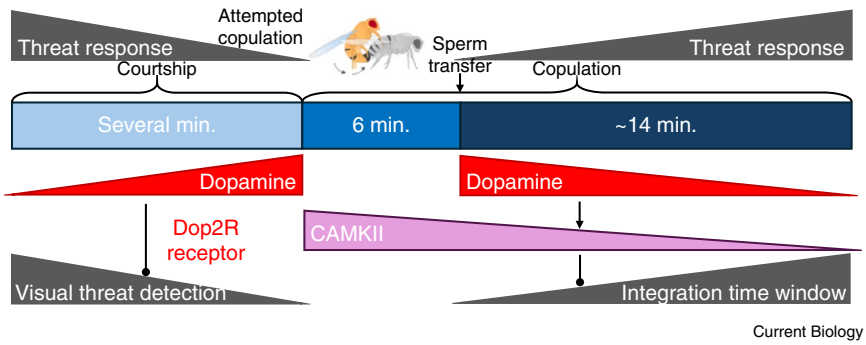

Figure 1. Mating state modulates threat responses in male flies.
During successful courtship, dopamine ramps up in the fly brain and inhibits visual threat detection via activation of Dop2R receptors in early visual system neurons[1]. After successful copulation and sperm transfer, flies slowly start responding again to threats. Dopamine decreases, reducing CAMKII activity and leading to a longer integration time window for dangerous stimuli[2]. (Fly image reused from[1] (CC BY 4.0).)

in neurons (also required for *Drosophila* learning[8]). CAMKII is already highly active in Corazonin neurons during the six-minute sperm transfer phase and is necessary for its precise timing[9]. By preventing the accumulation of cAMP via CAMKII, the activation of Corazonin neurons is delayed, so sperm transfer only happens six minutes into mating. During early copulation, CAMKII activity level changes via autophosphorylation. During final mating, dopamine modulates CAMKII activity in a different cell type, the copulation decision neurons (CDNs)[2]. These neurons in the ventral nerve cord (VNC) of the fly are necessary and sufficient for ending copulation. By modulating the level of CAMKII activity in these cells, Crickmore and colleagues show that CDNs can flexibly adapt their integration time window of threat information[2]. Towards the end of copulation, reduced dopamine levels lead to lower CAMKII activity in CDN neurons. This allows them to integrate threat information over a longer time window and to respond to the accumulation of weaker repeatedly pulsed stimuli. Dopamine might be broadly diffusing across the brain and the VNC during courtship. Where dopamine is released and why it is reduced in the VNC in the final stage of copulation is not known yet. Low dopamine levels after mating lead to a phase of satiety with a drastically reduced male mating drive[7]. Monoaminergic neuromodulators, such as dopamine and serotonin, are conserved across species and allow for flexible behavioral adaptations.

Potentially similar to the findings of Rezaval and colleagues, a recent study in rodents showed that activation of a serotonin receptor in the early visual system leads to reduced responses to external visual cues[10]. In the fly brain, serotonin is involved in expanding the coincidence time window of odor trace–shock conditioning[11], suggesting that the persistence of an olfactory trace is increased. Similarly to dopamine during courtship, serotonin modulates intracellular cAMP but keeps the neural circuit architecture unaffected.

The new study from Crickmore and colleagues[2] not only advances our understanding of the molecular implementation of temporal integration within a single neuron, but it also is one of the first demonstrations that neurons can change their integration capabilities. Simulation experiments fitted to experimental data reveal that the time constant increases during mating progression but not the weighting of the stimulus. This suggests that the connectivity of the neuron is hardwired, but that incoming signals are accumulated differently — an efficient mechanism to adjust neuronal output flexibly over minutes. The CAMKII pathway involved in this state-dependent integration is present in many cells; thus, many neurons might potentially act as integrators. A different cell-intrinsic molecular implementation of temporal integration happens in the fly learning center where a specific potassium channel controls cell activity levels over repeated odor stimuli exposures[12]. In vertebrates, temporal integration of visual information is distributed across many cells of the hindbrain during a dot-motion discrimination task[13]. In contrast to findings in *Drosophila*, this study (in vertebrates) suggests that slow time constants arise due to a specific neural circuit architecture consisting of many interconnected cells, but not necessarily through intrinsic molecular mechanisms[14,15]. Increased neural numbers in vertebrates could allow for a more distributed neural circuit implementation. Temporal integration might be a widespread property of many neurons or neural circuits but only performed in a specific state (such as hunger, stress), in different sensory contexts (such as socially exposed, isolated), or after learning[6,16].

There is a vast literature on computational modeling approaches of temporal integration and evidence accumulation[17], but the new findings[1,2] highlight the relevance of flexible neural activity. Neuromodulation affects not only weights or connections in a neural circuit but also the computations that are performed by single cells. Since evidence accumulation might be a widespread computation performed by many cell types, neural networks might consist of multiple connected integrator cells with complex interactions. Understanding these networks and how they change over time will be crucial to understanding brain function. Future studies across species will reveal whether multiple integrator cells or circuits temporally accumulate different types of information at different times and how they interact.

Current approaches in neuroscience focus on the analysis of available connectomes, which provide a snapshot of a hardwired neural circuit. The current studies in *Drosophila* courtship show that dopaminergic neuromodulation affects information processing in different neurons in different ways. Generally, neuromodulation can even take place via non-synaptic mechanisms[18,19]. This makes it harder to predict neural circuit function, which can change over time, just based on synaptic connectivity. Connectomics data also cannot reveal the cell-intrinsic biochemically implemented algorithms, as no specific circuit architecture seems to be required for that. It will thus be crucial to investigate

the distribution of molecular components and neuromodulators within cell types over time, contexts, and states, using transcriptomics or proteomics[20]. Combining such information with the connectivity map in flies is a promising direction to understanding the diverse functions of flexible hardwired neural circuits.

DECLARATION OF INTERESTS

The author declares no competing interests.

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Memory: Using the past to anticipate the future

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Memories can be decoded from brain responses and eye movements. A combined electroencephalogram–eyetracking study now shows that learning is marked by dynamic shifts in brain patterns and eye movements that go from remembering the past to anticipating the future.

Neuroimaging studies have long provided insight into how distinct brain regions and networks are differentially engaged by various cognitive states and task goals, as well as in rest[1,2]. Relatively recently, cognitive neuroscientists have leveraged multivariate analyses to examine issues of *representation*; i.e., what information is held in the mind, and how does that information change over time[3]? The power of such multivariate pattern analyses (MVPA) is in their 'mind-reading': MVPA affords researchers the ability to examine the patterns of brain activity that emerge seemingly 'spontaneously'[4,5]. Eyetracking provides a complementary tool for studying behavior: where and when the eyes look in the visual world can be guided by the seemingly spontaneous representations that are held in mind[6], even when there is nothing in the visual