Neuroscience: How the brain prioritizes behaviors

Raquel Barajas-Azpeleta[1,2], Ibrahim Tastekin[1,2], and Carlos Ribeiro[1,*]
[1]Champalimaud Centre for the Unknown, Lisbon, Portugal
[2]Authors contributed equally
*Correspondence: carlos.ribeiro@neuro.fchampalimaud.org
https://doi.org/10.1016/j.cub.2021.08.048

To optimize our choices, we need to prioritize among different goals. A recent study used a new *Drosophila* behavioral paradigm, bringing together conflicting behavioral choices in the context of different internal states and sensory cues, to provide foundational insights into the circuit mechanisms underlying how the brain prioritizes behavioral decisions.

Performing the optimal behavior at the right time is crucial for survival and reproductive success[1]. Given the uncertainty of living in a changing environment, animals have to deal with multiple, sometimes conflicting, motivations. For example, after a long day of work, you arrive home feeling very hungry and thirsty. What do you do first: eat or drink? With the tap ready to provide water, you might choose a quick drink. But what if your favorite meal was ready on the table? Now, what if your dog is about to eat your food? These different situations may change your choices. To make a behavioral decision, animals not only integrate internal needs, but also resource availability based on sensory cues, as well as the duration, consequences, and risks associated with a potential behavioral decision. Thus, animals need to weigh multiple interacting motivational drives to optimize their behavioral choices in response to dynamically changing internal and external variables. Different internal states could interact synergistically, competitively, or hierarchically to guide behavioral decisions[2,3] (Figure 1A).

Hunger, probably one of the strongest and ancestral motivational drives, can interact with other motivational drives, including social interactions[4], sleep[5], fear, and anxiety[6]. In flies, and likely other animals, protein deprivation and mating interact to synergistically increase the drive to eat proteinaceous foods, and therefore increase reproductive success[7]. However, where in the body these motivational drives are integrated and the underlying molecular and cellular mechanisms are poorly understood.

During the last decade, neural circuits and neuromodulatory mechanisms for motivational drives have been well studied in isolation using different model organisms[8–11]. However, how these neural-circuit mechanisms are coordinated to integrate different motivational drives and external stimuli to guide behavioral decisions remains elusive. What types of internally and externally generated signals does the brain integrate to prioritize behaviors? How plastic and dynamic is behavioral prioritization? Is it hardwired, or experience dependent? Answering these important questions requires behavioral paradigms capturing choice competition while enabling the dissection of the underlying molecular and neuronal circuit mechanisms.

In this issue of *Current Biology*, Cheriyamkunnel and colleagues[12] establish a novel behavioral paradigm in the fruit fly, *Drosophila melanogaster*, allowing them to study the outcome of conflicting motivational drives. Using this paradigm, they dissect the internal and external variables that lead to the prioritization of either initiation of feeding or courtship, and the underlying neural mechanisms. To achieve this, they modulated the hunger and mating states of male flies, and challenged them to choose between starting to eat from a drop of sugar or courting a female. They show that feeding initiation is prioritized over courtship initiation in males that are both sex- and food-deprived. Interestingly, the nutritional value of the food affects the choice: sex- and food-deprived males presented with a non-nutritious sugar and a female favored courting over feeding. The fly is therefore able to trade off both internal drives, process behaviorally relevant sensory stimuli accordingly, and then decide what behavior to initiate.

Next, the authors addressed how the prioritization between initiation of feeding or courting is implemented at the neuronal circuit level. Using a combination of neurogenetic circuit- and molecular manipulations as well as neurochemistry and imaging experiments, they showed that tyramine is a key neuromodulator mediating this decision. First, tyramine levels are modulated by the hunger state of the animal. Second, tyramine levels modulate two sucrose-responsive neuronal populations to promote the initiation of feeding or courting: a subset of tyramine-receptor (TyrR) neurons in the brain (TyR-PLP neurons), and the courtship-driving P1 neurons (Figure 1B). In a fed state, high levels of tyramine in the brain and female cues activate P1 neurons and inhibit TyrR neurons, leading to courtship initiation. However, in a starved state, lower levels of tyramine in the brain and food cues activating TyrR neurons will favor feeding initiation over courting. Together, these findings suggest that tyramine regulates feeding and mating behaviors antagonistically to flexibly prioritize feeding or mating depending on the hunger state and mating drive of the animal, as well as the present external cues.

This study clearly takes an important step towards exploring the neural mechanisms underlying the trade-off between conflicting motivational drives. Further questions, such as how starvation state is translated into tyramine-release dynamics through metabolic and endocrine signals, whether mating state is also integrated in other tyraminergic neurons, the neural elements that connect gustatory sensory cues to the Tyr-PLP neurons, and whether Tyr-PLP and P1

A

B

Current Biology
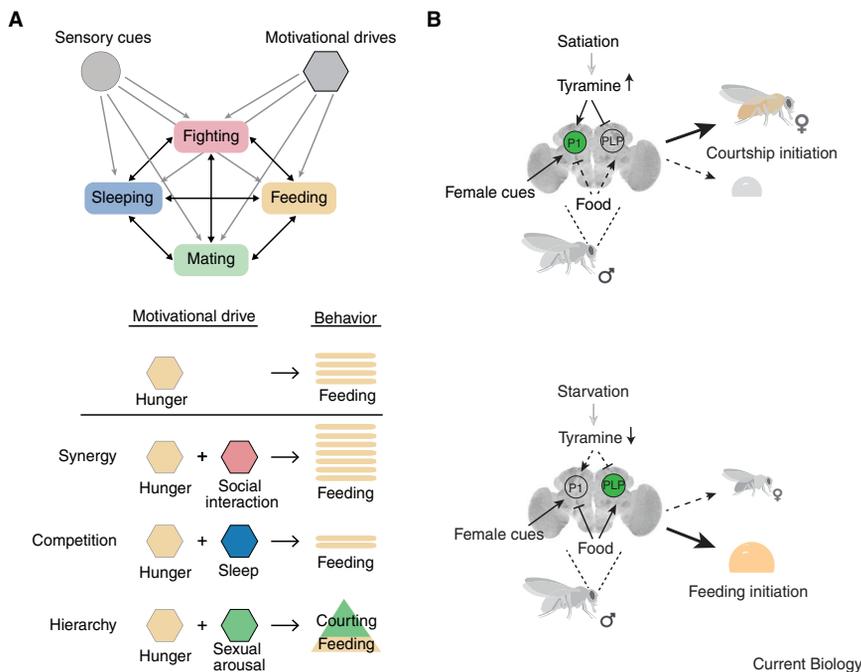
Figure 1. Motivational drives and sensory cues are integrated to prioritize different behaviors.
(A) Top: Schematic representation of the complex potential interactions between different sensory cues and motivational states to modulate an animal's behavior. Bottom: Different internal states can interact in several ways to shape behavioral decisions: synergistically, competitively, or in a hierarchical way. (B) The authors show that tyramine levels modulate two sucrose-responding neuronal populations to prioritize the initiation of feeding or courtship: a subset of tyramine-receptor (TyrR) neurons in the brain (TyR-PLP neurons), and the courtship-driving P1 neurons. Top: In the fed state, high levels of tyramine in the brain activate P1 neurons and inhibit TyrR neurons, leading to courtship initiation when female cues are present. Bottom: However, in a starved state, lower levels of tyramine in the brain activate TyrR neurons leading to the prioritization of feeding initiation over courtship when food cues are present. Together, these findings suggest that tyramine levels trade-off feeding and mating behaviors antagonistically to flexibly prioritize feeding or mating depending on the hunger state and mating drive of the animal as well as the present external sensory cues.

neurons directly interact with each other are obvious next steps which can be tackled using this system.

With their work, the authors show once more why *Drosophila* is such a powerful system to mechanistically explore complex circuit neuroscience questions, like how the brain integrates internal and external signals to deal with different, often conflicting motivations and chooses specific actions. Further work should yield important mechanistic insights given that flies exhibit complex motivations and behavioral manifestations that interact in non-linear ways (e.g. prioritization, synergistic enhancement), have conserved neuromodulatory pathways for motivations[8,13,14], and offer unmatched genetic access to monitor and manipulate the activity and molecular processes in specific neurons during behavior. Together with the availability of a full connectome[15,16], the fly therefore

remains a very attractive system to provide mechanistic insights into the intricacies of the brain.

Importantly, this study shows the power of well-designed behavioral paradigms for the functional dissection of complex neuronal processes. Similar behavioral designs have the potential to widen our understanding of conflicting behaviors. First, using this setting, it is possible to explore other pairs of motivational conflicts such as drinking vs. mating, and feeding vs. escaping a threat (risk-taking), as well as multitasking (more than two conflicting motivational drives). One could also address how fixed a decision is once it has been made. For instance, what would a starved male fly do if it already decided to court a female, but it is suddenly presented with a drop of sugar? A further important and poorly explored question is how flexible behavioral prioritizations are. Do animals

of the same species possess the same hierarchy of needs, or do hierarchies vary between individuals? How does the personal experience of the animal impinge on these priorities? How do learning mechanisms act at the level of priorities? For example, how does a constantly sexually rejected male behave? What do animals with pathological metabolic states, like obesity, prefer? Given the detailed knowledge of the neuronal substrates of learning and memory, and the conservation of the mechanistic basis of pathological states, the field is well positioned to provide compelling answers to these questions.

Cheriyamkunnel and colleagues do a brilliant job establishing an experimental framework to look at the mechanisms driving behavioral prioritization. Deeper insight could be gained by embracing a more quantitative analysis of behavior paired with more naturalistic scenes. While reducing the complexity of the analysis facilitates understanding to some extent, one cannot help wondering if animals really have such a binary view of decision-making, as suggested by the current literature. A key question for example is what happens if animals encounter different stimuli in the same place, at the same time. For example, a potential mate can be located very close to the food source. Would an animal mate and eat at the same time? This also raises an interesting question about behaviors in general: can we consider a particular behavior as a discrete set of actions, rather than a continuous action? Indeed, an animal could be nibbling at a food source, stop to take some sips from a drink, and then go back to eating. What is the minimum display to consider an action a behavior, or to consider an action part of a particular behavior? While this will require the development of further behavioral paradigms with high temporal and spatial resolution, it will also be important to develop and embrace more complex, and likely probabilistic, conceptual frameworks to describe and be able to explain decision-making in animals, including humans.

Finally, while we neuroscientists like to think of the brain as computing in isolation, it is clear that we cannot achieve a meaningful understanding of the mechanisms guiding complex decisions,

and their adaptation to the needs of the animal, without embracing the interactions between the brain and the body. For instance, organ systems use non-neuronal systems to compute the current state of the animal and exchange this information using inter-organ communication systems. Incorporating these organism-level interactions, and how the brain interplays with these, is an important but challenging endeavor. This is exactly where tractable animal systems like invertebrates shine. They are complex enough to rely on such organism-level interactions with the brain while allowing for a mechanistic interrogation of these systems. In summary, studies like the one by Cheriyamkunnel and colleagues, in which complex questions are made tractable using smart experimental designs, paired with the tools generated by an active and collaborative community, will break the boundaries of understanding intricate relationships between internal states, sensory stimuli, and neuronal molecular and circuit mechanisms that at the end drive apparently simple, but actually elaborate behaviors.

REFERENCES

1. Münch, D., Ezra-Nevo, G., Francisco, A.P., Tastekin, I., and Ribeiro, C. (2020). Nutrient homeostasis — translating internal states to behavior. Curr. Opin. Neurobiol. 60, 67–75.

2. Sutton, A.K., and Krashes, M.J. (2020). Integrating hunger with rival motivations. Trends Endocrinol. Metab. 31, 495–507.

3. Burnett, C.J., Funderburk, S.C., Navarrete, J., Sabol, A., Liang-Guallpa, J., Desrochers, T.M., and Krashes, M.J. (2019). Need-based prioritization of behavior. eLife 8, e44527.

4. Jennings, J.H., Kim, C.K., Marshel, J.H., Raffiee, M., Ye, L., Quirin, S., Pak, S., Ramakrishnan, C., and Deisseroth, K. (2019). Interacting neural ensembles in orbitofrontal cortex for social and feeding behaviour. Nature 565, 645–649.

5. Keene, A.C., Duboué, E.R., McDonald, D.M., Dus, M., Suh, G.S.B., Waddell, S., and Blau, J. (2010). Clock and cycle limit starvation-induced sleep loss in Drosophila. Curr. Biol. 20, 1209–1215.

6. Burnett, C.J., Li, C., Webber, E., Tsaousidou, E., Xue, S.Y., Brüning, J.C., and Krashes, M.J. (2016). Hunger-driven motivational state competition. Neuron 92, 187–201.

7. Walker, S.J., Goldschmidt, D., and Ribeiro, C. (2017). Craving for the future: the brain as a nutritional prediction system. Curr. Opin. Insect Sci. 23, 96–103.

8. Kim, S.M., Su, C.-Y., and Wang, J.W. (2017). Neuromodulation of innate behaviors in Drosophila. Annu. Rev. Neurosci. 40, 327–348.

9. Taghert, P.H., and Nitabach, M.N. (2012). Peptide neuromodulation in invertebrate model systems. Neuron 76, 82–97.

10. Picciotto, M.R., Higley, M.J., and Mineur, Y.S. (2012). Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. Neuron 76, 116–129.

11. Palmer, C.R., and Kristan, W.B. (2011). Contextual modulation of behavioral choice. Curr. Opin. Neurobiol. 21, 520–526.

12. Cheriyamkunnel, S.J., Rose, S., Jacob, P.F., Blackburn, L.A., Glasgow, S., Moorse, J., Winstanley, M., Moynihan, P.J., Waddell, S., and Rezaval, C. (2021). A neuronal mechanism controlling the choice between feeding and sexual behaviors in Drosophila. Curr. Biol. 31, 4231–4245.

13. Asahina, K., Watanabe, K., Duistermars, B.J., Hoopfer, E., González, C.R., Eyjólfsdóttir, E.A., Perona, P., and Anderson, D.J. (2014). Tachykinin-expressing neurons control male-specific aggressive arousal in Drosophila. Cell 156, 221–235.

14. Fadda, M., Hasakiogullari, I., Temmerman, L., Beets, I., Zels, S., and Schoofs, L. (2019). Regulation of feeding and metabolism by Neuropeptide F and Short Neuropeptide F in invertebrates. Front. Endocrinol. 10, 64.

15. Dorkenwald, S., McKellar, C., Macrina, T., Kemnitz, N., Lee, K., Lu, R., Wu, J., Popovych, S., Mitchell, E., Nehoran, B., et al. (2020). FlyWire: Online community for whole-brain connectomics. bioRxiv. https://doi.org/10.1101/2020.08.30.274225.

16. Scheffer, L.K., Xu, C.S., Januszewski, M., Lu, Z., Takemura, S., Hayworth, K.J., Huang, G.B., Shinomiya, K., Maitlin-Shepard, J., Berg, S., et al. (2020). A connectome and analysis of the adult Drosophila central brain. eLife 9, e57443.

Cell-size control: Chromatin-based titration primes inhibitor dilution

Shicong Xie and Jan M. Skotheim
Department of Biology, Stanford University, Stanford, CA 94305, USA
Correspondence: xies@stanford.edu (S.X.), skotheim@stanford.edu (J.M.S.)
https://doi.org/10.1016/j.cub.2021.08.031

Cell growth can drive progression into the cell cycle by diluting a diverse set of cell-cycle inhibitors in yeast, animal, and plant cells. Inhibitor dilution mechanisms implement cell-size control when large and small cells inherit a similar number of inhibitor molecules, and new work shows that these mechanisms in plant cells include specific degradation and chromatin-partitioning components.

Growth, form, and function are typically linked. The most fundamental feature of organismal form is their size, as J.B.S. Haldane succinctly put it: "The most obvious differences between different animals are differences of size... it is easy to show that a hare could not be as large as a hippopotamus, or a whale as small as a herring. For every type of animal there is a most convenient size"[1]. However, while the functions of specific organism sizes and morphologies have been elucidated