https://doi.org/10.1051/bioconf/202516601005

Multisensory integration in Drosophila

Shiqi Tang[1,a,#], Canran Zhou[2,b,#], Youxiang Cheng[3,*,#]

[1]College of Life Sciences and Technology, Tongji University, Shanghai, 200092, China
[2]Department of Biological Sciences, University of Toronto Scarborough, Toronto, M1C 1A4, Canada
[3]Life science college, Sun Yat-Sen University, Guangzhou, 510275, China

Abstract. Multisensory integration (MSI) is a crucial process by which organisms combine information from multiple senses to enhance their perception and adapt to the environment. This review focuses on MSI in Drosophila, an ideal model organism due to its well-characterized neural circuitry and genetic tractability. We first describe the five main sensory modalities (vision, olfaction, gustation, mechanosensation, and thermosensation) and how they contribute to the Drosophila's behavior. Then, we discuss the basic models of MSI, including feedback, convergence, gating, parallelism, and association. The underlying neural circuits involved in MSI, such as those related to foraging, navigation, and feeding behaviors, are also explored. Additionally, we highlight the role of neuromodulators in regulating MSI and its functional significance in enhancing information acquisition and decision-making. Overall, understanding MSI in Drosophila provides valuable insights into the mechanisms underlying complex behaviors and serves as a foundation for further studies in other organisms, ultimately helping us better understand how the nervous system processes and integrates multisensory information.

1. Introduction

Our senses are how we understand the world. We build sensory relations and integrate multisensory inputs that come from the surrounding environment to establish an overall image and to better adapt to the world[1]. The complex nervous system is unconsciously able to integrate, arrange, and grade sensory inputs from various sources, and enable us to respond in time. Therefore, it is valuable to understand the way the nervous system integrates various sensory signals and the specific mechanisms behind it.

It is known that many diseases are related to dysfunction of multisensory integration (MSI), a specific multisensory processing where redundant sensory information is optimally integrated to result in a multisensory response significantly different than their unisensory correspondence. Autism Spectrum Disorder (ASD) patients are considered to have a longer multisensory temporal binding window (TBW) than normal people[2]. Time plays a vital role in MSI mechanism[3]. TBW defines the interval between the stimuli for which we establish relations. ASD patients are relatively unable to relate stimuli together, making them always overreact or lack appropriate responses, thus showing autism[4, 5]. Other diseases such as Anorexia Nervosa (AN) show a situation in which patients have visual perceptual body-size distortion[6]. These diseases greatly affect the lives of patients and increase the government's medical expenditure and social burden.

It's challenging to directly investigate the multisensory integration of humans poses significant challenges due to the complex neuron circuits, countless synapses and neurons, and strict ethical order. In this case, researchers turn to Drosophila, which has a complete neuron circuit connectome[7]. Besides, Drosophila is easy to culture and is accessible for gene editing, which makes it a suitable model organism for neuroscience researchers to conduct experiments on neural circuits and molecular mechanisms. Therefore, in this review, we will tease out the sensory pathways in Drosophila, and then we will attempt to refine general models of MSI. After that, we will summarize the current research on the neural circuits and neuromodulators of MSI in Drosophila and finally discuss the functional consequences of MSI in behavior and future direction.

2. Drosophila performs multisensory integration

For almost every animal in this world, life is not just a single sensory experience. Not only do animals need to constantly avoid traps and predators during their survival, they also need to obtain the nutrients to sustain life. In order to be able to better seek benefits and avoid harm, animals have evolved a variety of senses, and these sensory signals are well combined to enhance the level of reception of certain information. In the case of insects, hearing has evolved multiple times to adapt to complex environments, and olfaction and vision have also evolved in complex and divergent ways[8–12]. During the process

---

[a]CandyTang@tongji.edu.cn, [b]canran.zhou@mail.utoronto.ca,
[*]Corresponding author: Chengyx9@mail2.sysu.edu.cn
[#]co-first authors

of evolution, interaction and signal integration between multiple senses is unavoidable. Nowadays, more and more reports have revealed the cross-sensory multimodal role of proteins that function in different sensory layers. For example, rhodopsin, a protein essential for maintaining vision, can produce mechanosensory effects independent of photophysiological processes[13]; in addition, rhodopsin has been reported to play a role in conducting bitter taste in gustatory receptor neurons of Drosophila[14]. This suggests that the molecular mechanisms underlying different senses may be similar in some degree.

Before describing the multisensory integration of Drosophila, it is necessary to describe the senses and some sensory preferences separately. The senses of the Drosophila are generally thought to consist of the following five components: vision, olfaction, gustation, mechanosensation, and thermosensation.

2.1. Vision

Drosophila are able to perceive spatial and directional information through vision, which plays an important role in finding food and avoiding predation. Drosophila have obvious phototaxis, which is an underlying logic for studying their sensory behavior[15]. It is worth noting that Drosophila tend to fly toward long stripes rather than small spots, which helps them find the right plant habitats and feeding grounds rather than colliding with predators and other objects[16]. Additionally, it is interesting that although larvae do not have the anatomically typical eye structure as Drosophila do, they still have a marked phototaxis or light avoidance mediated by relevant photosensory structures and neurons[17–19].

2.2. Olfaction

The sense of olfaction enables Drosophila to adapt their behavior according to the odors in their environment, particularly in relation to foraging and reproducing activities. In the process of odor recognition, Drosophila can compare the signal strength of their two antennae to determine the odor concentration gradient[20]. Previous studies have shown that the odor receptor gene Or83b, which is highly conserved and widely expressed in the neurons of Drosophila, is essential for olfaction[21, 22]. Drosophila larvae sense odor information in different directions by sweeping their heads[23]. By activating reward neurons in the brain, Drosophila larvae are even able to learn to overcome their innate aversion to carbon dioxide gas[24].

2.3. Gustation

While remote food detection is generally done by the olfactory and visual systems, the quality of the food is assessed by the Drosophila gustatory system, all before the action of feeding. Taste neurons are abundant in several organs of the Drosophila, such as the legs, the edges of wings, the labial palp of the proboscis labellum, the internal mouthpart organs, and even the ovipositor[25]. Drosophila are known to prefer foods high in sugar, but startlingly, they can also taste bitter. It has been found that some bitter compounds can effectively inhibit the activation of sugar-sensing neurons in Drosophila[26]. Since the developmental genus of Drosophila is completely metamorphosed, it is conceivable that the larvae have almost completely different gustation organs and neural circuits from the adults[27]. The dorsal organ (DO), the terminal organ (TO), and the ventral organ (VO) are responsible for most of the larva's taste sensations, and the gustation neural circuits of larvae are simpler[27].

2.4. Mechanosensation

The courtship behavior of Drosophila depends on the courtship song produced by their wings[28]. The frequency spectrum of these songs is right in the fruit fly hearing range. The presence of a large number of chordotonal stretch-receptor neurons in the Drosophila antenna converts antenna displacement into electric current[29]. Besides, the mechanosensory structure of the antennae can also respond to mechanical signals brought by air currents, activating different areas of the brain compared with their sound perception[30]. Harmful mechanosensory stimuli induce freezing behavior in drosophila adults but often escape behavior in larvae[31, 32].

2.5. Thermosensation

Drosophila have a strong temperature preference around 24°C, and they will attempt to avoid both excessively high or low temperature stimulations[33]. While Drosophila larvae prefer temperatures of 18°C[34]. Interestingly, Drosophila larvae have a stronger aversion to heat than to cold[35], so when higher heat is used to stimulate fruit fly larvae, it activates their flight response[32]. Drosophila have sensory neurons in its antennae that respond to heat and cold, and some of its internal neurons also sense temperature [36–38]. Similar to the adults, larvae have heat sensors on the anterior tip of their heads[32].

In a complex real-world environment, various behaviors of Drosophila depend on the integration of multiple sensory signals. Based on the current understanding of various sensory mechanisms in Drosophila melanogaster, it is possible to study the mechanisms of integration of different sensory signals.

3. Basic models of multisensory integration

In general, the underlying logic of multisensory integration is the integration of signals from two different senses. Based on the integration of two senses, there are five main ways: feedback, convergence, gating, parallelism, and association (Figure 1).

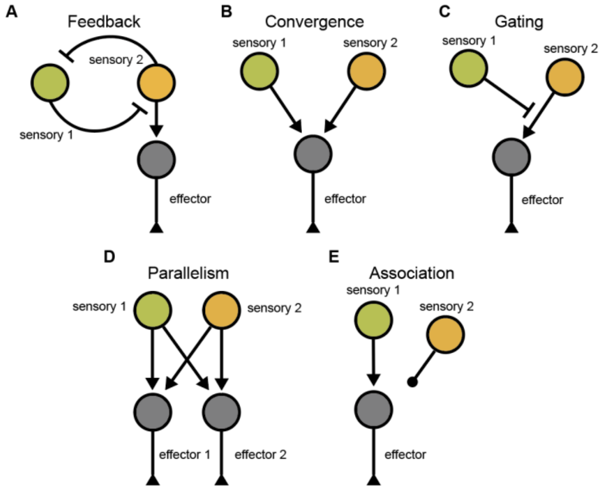

Figure 1. The underlying paradigm of sensory inputs

A-E. Represents the possible patterns of two different sensory signal inputs. The green sphere represents sensory input 1, the yellow sphere represents sensory input 2, and the gray sphere represents the behavioral effector. The pointed end arrow indicates the direction of the signal, the flat end arrow indicates the interaction between sensory inputs, and the round end indicates that the input transmits signals through indirect means, such as neuromodulators.

There may be a certain degree of feedback adjustment of input from different senses. Most of the feedback regulation presents a typical inhibition pattern, in which the input of one sense has a masking effect on the input of another sense, that is, a single sensory stimulus of sufficient intensity can play a decisive role.

The convergent enhancement of the senses is more common. For example, the use of thermal and acoustic stimuli (mechanosensation) to simulate the bites of wasp and the sound of wing flaps to stimulate Drosophila larvae significantly enhanced their escape behavior when both stimuli were present, compared to only one stimulus[32]. In this model, multiple different inputs to sensory stimuli can enhance the output of the same effect neuron, and so it is likely to have a synergistic effect on the enhancement of a particular behavior in an individual. Besides, olfaction and view also indicate convergent enhancement in Drosophila. The combination of both senses leads to better navigation and foraging than a single sense.[39]

The gating model shows that the input-output behavior of one sense needs to be based on the input of another sense signal. Under the background of neurobiology, sensory gating refers to the mandatory process of inhibition in early information processing. Odor attraction alone is not sufficient to initiate feeding behavior in Drosophila, but taste gating effectively initiates feeding. It's worth noting that, timeliness can cause the two senses to interfere with each other. When the two senses are out of sync, the senses that would otherwise complement each other to achieve convergence interfere with each other. To some extent this fits into a reciprocal gating model.

Parallel inputs appear in models of multiple effector neurons, and the distribution of signal inputs from the two senses occupies different proportions in different effectors. What this model emphasizes is that the input of different sensory stimuli to different effector neurons is in different proportions, thus regulating individual behavior.

In the association model, a form of sensory involvement may be indirect, which is likely to involve neuromodulators. Through the action of neuromodulators, this sense can enhance or inhibit the activation of effector neurons to a certain extent. For example, tachykinin-related peptides (TKRPs) from Drosophila melanogaster are a good example of neuromodulators. In the absence of TKRPs, flies were less sensitive to certain odors and had difficulty distinguishing odor concentration changes[39].

4. Circuits underlying multisensory integration

With overwhelming evidence for the significance of MSI, recently researchers are turning their focus onto the underlying circuits of MSI. These complicated neural circuits facilitate the processing of sensory information from multiple modalities and thus are essential for enabling Drosophila to respond appropriately to complex environmental stimuli. Based on the connectome map of the brain of Drosophila and its larvae has been completed, which is the foundation for a clearer understanding of the neural circuitry of MSI[7, 40].

The MSI involved in foraging and navigation in Drosophila is a relatively well-studied area. Drosophila relies on smell and sight to locate food sources during foraging. Interestingly, studies have shown that paired appetitive food odor can increase the optomotor response of drosophila. This is because octopaminergic (OA) neurons activated by olfactory signals transmit signals to the wide-field motion-detecting neuron (Hx), which detects visual stimuli, thus realizing cross-modal transmission of signals[41]. In the wind-directed olfactory circuitry of Drosophila, the integration of mechanical sensory input with olfactory input was also found. The results indicate that there may be multiple sites of integration of mechanical perception and olfactory perception, such as hΔC neurons, which connect fan-shaped body (FB) tangential inputs (integrated odor value) and FB columnar inputs (wind-direction), furthermore, the lateral accessory lobe (LAL) region also receives wind direction and odor signal inputs[40].

There is also multisensory integration in the feeding behavior of Drosophila[42]. Yeast is one of the nutritional sources for them, and its odor contains various volatile compounds. Related studies have shown that simultaneous olfactory and mechanosensory inputs significantly influence guest-induced feeding behavior called beak extension reflex (PER). In this process, olfactory and mechanical information are mediated by antennal Or35a neurons and leg hair plate mechanosensory neurons, respectively. All three sensory modes (taste, smell, and mechanical) must be activated simultaneously to enhance PER, and sensory stimuli alone or in pairs cannot achieve this effect[43]. This implies that some mechanism in the neural circuit allows these multisensory inputs to work together to regulate the feeding decisions. However, the specific neural circuitry remains to be explored. Further exploration of the neural circuits underlying these behaviors will help us to better understand the physiological foundation and underlying logic of multisensory integration.

5. Neuromodulators regulate multisensory integration by modulating the state of neural circuits

Flexible modifications in the output of Drosophila neural networks facilitate the regulation of their behavior, with neuromodulators playing a crucial role in this process. Neuromodulators such as neuropeptides, hormones, and biogenic amines can alter synaptic function and neuronal dynamics through intracellular signaling cascades[44]. Besides, neuromodulators usually have slower response kinetics and long-lasting effects in the process of neuronal regulation, they play a unique role in multisensory regulation, which makes them unreplaceable for performing normal life activities of Drosophila[45].

When Drosophila perform complex behaviors, they are often guided by the fusion of multi-sensory signals to make motor decisions. During courtship, for example, male Drosophila exhibit a coherent and complex set of behaviors in response to signals from different senses, especially the neuromodulator called pheromones[46, 47]. The typical neuromodulator dopamine has considerable control over the sexually driven behavior of Drosophila. With repeated mating, male courtship frequency decreases, and this reproductive satisfaction is caused by decreased dopaminergic activity in the superior medial protocerebrum (SMPa)[48]. It was also found that fruitless (fru)/doublesex (dsx)-coex-pressing neuronal clusters (P1 neurons) function in SMPa[49]. In addition, P1 neurons are also important nodes for the convergence of taste and olfactory pheromone circuits in drosophila courtship behavior[50].

For female Drosophila, their preferences for food and spawning sites change during reproduction depending on the state, such as increasing the female's interest in specific beneficial nutrients: polyamines such as spermine and putrescine[51, 52]. It is found that in pregnant females, polyamine attraction is modulated by G-protein-coupled receptor, sex peptide receptor (SPR), and myoinhibitory peptides (MIPs), which directly act on neurons responsible for polyamine detection of smell and taste[51]. In other words, these neuromodulators regulate the input of both smell and taste signals to enable Drosophila to display more gestational food preferences.

Moreover, even if the Drosophila are not engaged in specific reproductive or mating activities, the effects of some neuromodulators can also affect multisensory input. Dopamine regulates vision, gustation, and thermosensation in Drosophila[53–55], and serotonin can also regulate gustation preference and spatial perception[56, 57]. However, the specific neural circuit mechanism of how neuromodulators such as dopamine and serotonin play a role in the multisensory integration of Drosophila still needs further investigation.

6. Functional significance of multisensory integration

Overall, we review MSI behaviors in Drosophila melanogaster in various scenarios, possible underlying mechanisms, and basic integration models. These studies suggest that MSI behavior can occur either through direct synaptic contact (neural circuits) or through non-synaptic connections (neuromodulators).

We believe that MSI enables Drosophila to refine complex environmental information to make decisions that are suitable for their survival. In addition, MSI was able to enhance the Drosophila's information acquisition ability to improve their decision reaction time and the efficiency of processing information. More importantly, the presence of MSI greatly increases the complexity and flexibility of the output of the results, allowing the Drosophila to adapt more quickly to the changing external environment.

Interestingly, in some studies, researchers linked MSI to learning or memory in Drosophila[32, 58]. This allows Drosophila to further integrate sensory inputs with the role of past experiences, suggesting that the mechanisms of MSI are dynamic and can adapt to external stimuli.

In summary, we believe that MSI helps to produce the most favorable living conditions in an environment with complex content and spatial and temporal characteristics.

7. Conclusion

Over the past century, studies on MSI have focused on various species, ranging from primitive species such as C. elegans[59, 60] to mammals like rats[61], cats[62], and monkeys. Though our ultimate goal is to figure out the MSI mechanism of human beings, due to moral and ethical limitations, we had to search for more accessible biological materials for the experiments. Thus, we choose Drosophila as the module because of its accessibility, particularity, and representativeness.

This review comprehensively elaborates on multisensory integration (MSI) in Drosophila. It commences by introducing the five primary sensory modalities in Drosophila, namely vision, olfaction, gustation, mechanosensation, and thermosensation, and elucidates their contributions to the Drosophila's behavior. Subsequently, it expounds on the five fundamental models of MSI, including feedback, convergence, gating, parallelism, and association, highlighting their significance in enhancing the fly's ability to make survival decisions, acquire information, and adapt to the environment.

Nevertheless, current research predominantly focuses on the integration mechanisms of two senses. Future investigations should explore the integration pathways of more sensory inputs and the underlying genetic mechanisms. The research on Drosophila provides a foundation for understanding the decision-making mechanisms in complex environments and serves as a basis for studies in other species, especially humans.

Besides, we haven’t compared our studies with other species, which can enhance our overall understanding of

MSI mechanism, providing a probability to apply these studies to research on humans. The comparison between Drosophila, C. elegans, and humans can establish an MSI research network that can better link the previously isolated studies about MSI in different species.

Overall, comprehending the mechanisms of multisensory fusion in Drosophila enables us to gain a more profound understanding of how complex external environments affect decision-making in organisms and provides a foundation for further investigations into the nervous systems of other higher animals, such as mammals.

Acknowledgement

Shiqi Tang, Canran Zhou and Youxiang Cheng contributed equally to this work and should be considered co-first authors.

References

1. Wallace MT, Woynaroski TG, Stevenson RA. Multisensory Integration as a Window into Orderly and Disrupted Cognition and Communication. Annu Rev Psychol. 2020;71:193–219.
2. Wallace MT, Stevenson RA. The construct of the multisensory temporal binding window and its dysregulation in developmental disabilities. Neuropsychologia. 2014;64:105–23.
3. Meredith M, Nemitz J, Stein B. Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. J Neurosci. 1987;7:3215–29.
4. Thye MD, Bednarz HM, Herringshaw AJ, Sartin EB, Kana RK. The impact of atypical sensory processing on social impairments in autism spectrum disorder. Developmental Cognitive Neuroscience. 2018;29:151–67.
5. Gaudio S, Brooks SJ, Riva G. Nonvisual Multisensory Impairment of Body Perception in Anorexia Nervosa: A Systematic Review of Neuropsychological Studies. PLOS ONE. 2014;9.
6. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Bischoff-Grethe A. Nothing tastes as good as skinny feels: the neurobiology of anorexia nervosa. Trends in Neurosciences. 2013;36:110–20.
7. Winding M, Pedigo BD, Barnes CL, Patsolic HG, Park Y, Kazimiers T, et al. The connectome of an insect brain. Science. 2023;379:eadd9330.
8. Göpfert MC, Hennig RM. Hearing in Insects. Annual Review of Entomology. 2016;61 Volume 61, 2016:257–76.
9. Hansson BS, Stensmyr MC. Evolution of Insect Olfaction. Neuron. 2011;72:698–711.
10. Pisani D, Rota-Stabelli O, Feuda R. Sensory Neuroscience: A Taste for Light and the Origin of Animal Vision. Current Biology. 2020;30:R773–5.
11. Van Der Kooi CJ, Stavenga DG, Arikawa K, Belušič G, Kelber A. Evolution of Insect Color Vision: From Spectral Sensitivity to Visual Ecology. Annu Rev Entomol. 2021;66:435–61.
12. Hardcastle BJ, Krapp HG. Evolution of Biological Image Stabilization. Current Biology. 2016;26:R1010–21.
13. Senthilan PR, Piepenbrock D, Ovezmyradov G, Nadrowski B, Bechstedt S, Pauls S, et al. Drosophila Auditory Organ Genes and Genetic Hearing Defects. Cell. 2012;150:1042–54.
14. Leung NY, Thakur DP, Gurav AS, Kim SH, Di Pizio A, Niv MY, et al. Functions of Opsins in Drosophila Taste. Current Biology. 2020;30:1367-1379.e6.
15. McEwen RS. The reactions to light and to gravity in Drosophila and its mutants. J Exp Zool. 1918;25:49–106.
16. Maimon G, Straw AD, Dickinson MH. A Simple Vision-Based Algorithm for Decision Making in Flying Drosophila. Current Biology. 2008;18:464–70.
17. Xiang Y, Yuan Q, Vogt N, Looger LL, Jan LY, Jan YN. Light-avoidance-mediating photoreceptors tile the Drosophila larval body wall. Nature. 2010;468:921.
18. Kane EA, Gershow M, Afonso B, Larderet I, Klein M, Carter AR, et al. Sensorimotor structure of Drosophila larva phototaxis. Proc Natl Acad Sci U S A. 2013;110:E3868–77.
19. de Andres-Bragado L, Mazza C, Senn W, Sprecher SG. Statistical modelling of navigational decisions based on intensity versus directionality in Drosophila larval phototaxis. Sci Rep. 2018;8:11272.
20. Gaudry Q, Hong EJ, Kain J, de Bivort BL, Wilson RI. Asymmetric neurotransmitter release enables rapid odor lateralization in Drosophila. Nature. 2013;493:424–8.
21. Larsson MC, Domingos AI, Jones WD, Chiappe ME, Amrein H, Vosshall LB. Or83b Encodes a Broadly Expressed Odorant Receptor Essential for Drosophila Olfaction. Neuron. 2004;43:703–14.
22. Ditzen M, Pellegrino M, Vosshall LB. Insect Odorant Receptors Are Molecular Targets of the Insect Repellent DEET. Science. 2008;319:1838–42.
23. Gershow M, Berck M, Mathew D, Luo L, Kane EA, Carlson JR, et al. Controlling airborne cues to study small animal navigation. Nat Methods. 2012;9:290–6.
24. Lesar A, Tahir J, Wolk J, Gershow M. Switch-like and persistent memory formation in individual Drosophila larvae. eLife. 10:e70317.
25. Scott K. Gustatory Processing in Drosophila melanogaster. Annual Review of Entomology. 2018;63 Volume 63, 2018:15–30.
26. Weiss LA, Dahanukar A, Kwon JY, Banerjee D, Carlson JR. The Molecular and Cellular Basis of Bitter Taste in Drosophila. Neuron. 2011;69:258–72.

27. Apostolopoulou AA, Rist A, Thum AS. Taste processing in Drosophila larvae. Front Integr Neurosci. 2015 Oct 13;9:50.
28. Greenspan RJ, Ferveur J-F. COURTSHIP IN DROSOPHILA. Annual Review of Genetics. 2000;34 Volume 34, 2000:205–32.
29. Albert JT, Göpfert MC. Hearing in Drosophila. Current Opinion in Neurobiology. 2015;34:79.
30. Yorozu S, Wong A, Fischer BJ, Dankert H, Kernan MJ, Kamikouchi A, et al. Distinct sensory representations of wind and near-field sound in the Drosophila brain. Nature. 2009;458:201–5.
31. Matsuo E, Kamikouchi A. Neuronal encoding of sound, gravity, and wind in the fruit fly. J Comp Physiol A. 2013;199:253–62.
32. Ohyama T, Schneider-Mizell CM, Fetter RD, Aleman JV, Franconville R, Rivera-Alba M, et al. A multilevel multimodal circuit enhances action selection in Drosophila. Nature. 2015;520:633–9.
33. Sayeed O, Benzer S. Behavioral genetics of thermosensation and hygrosensation in Drosophila. Proceedings of the National Academy of Sciences. 1996;93:6079–84.
34. Liu L, Yermolaieva O, Johnson WA, Abboud FM, Welsh MJ. Identification and function of thermosensory neurons in Drosophila larvae. Nat Neurosci. 2003;6:267–73.
35. Zars T. Hot and cold in Drosophila larvae. Trends in Neurosciences. 2003;26:575–7.
36. Ni L, Bronk P, Chang EC, Lowell AM, Flam JO, Panzano VC, et al. A gustatory receptor paralog controls rapid warmth avoidance in Drosophila. Nature. 2013;500:580–4.
37. Gallio M, Ofstad TA, Macpherson LJ, Wang JW, Zuker CS. The Coding of Temperature in the Drosophila Brain. Cell. 2011;144:614–24.
38. Hamada FN, Rosenzweig M, Kang K, Pulver SR, Ghezzi A, Jegla TJ, et al. An internal thermal sensor controlling temperature preference in Drosophila. Nature. 2008;454:217–20.
39. Matheson AMM, Lanz AJ, Medina AM, Licata AM, Currier TA, Syed MH, et al. A neural circuit for wind-guided olfactory navigation. Nat Commun. 2022;13:4613.
40. Wasserman SM, Aptekar JW, Lu P, Nguyen J, Wang AL, Keles MF, et al. Olfactory Neuromodulation of Motion Vision Circuitry in Drosophila. Current Biology. 2015;25:467–72.
41. Miroschnikow A, Schlegel P, Pankratz MJ. Making Feeding Decisions in the Drosophila Nervous System. Curr Biol. 2020;30:R831–40.
42. Oh SM, Jeong K, Seo JT, Moon SJ. Multisensory interactions regulate feeding behavior in Drosophila. Proceedings of the National Academy of Sciences. 2021;118:e2004523118.
43. Bargmann CI. Beyond the connectome: How neuromodulators shape neural circuits. BioEssays. 2012;34:458–65.
44. Kim SM, Su C-Y, Wang JW. Neuromodulation of Innate Behaviors in Drosophila. 2017 Jul 25;40:327-348.
45. Ejima A, Smith BPC, Lucas C, Van Der Goes Van Naters W, Miller CJ, Carlson JR, et al. Generalization of Courtship Learning in Drosophila Is Mediated by cis-Vaccenyl Acetate. Current Biology. 2007;17:599–605.
46. Thistle R, Cameron P, Ghorayshi A, Dennison L, Scott K. Contact Chemoreceptors Mediate Male-Male Repulsion and Male-Female Attraction during Drosophila Courtship. Cell. 2012;149:1140–51.
47. Zhang SX, Rogulja D, Crickmore MA. Dopaminergic Circuitry Underlying Mating Drive. Neuron. 2016;91:168–81.
48. Kimura K, Hachiya T, Koganezawa M, Tazawa T, Yamamoto D. Fruitless and Doublesex Coordinate to Generate Male-Specific Neurons that Can Initiate Courtship. Neuron. 2008;59:759–69.
49. Clowney EJ, Iguchi S, Bussell JJ, Scheer E, Ruta V. Multimodal Chemosensory Circuits Controlling Male Courtship in Drosophila. Neuron. 2015;87:1036–49.
50. Hussain A, Üçpunar HK, Zhang M, Loschek LF, Grunwald Kadow IC. Neuropeptides Modulate Female Chemosensory Processing upon Mating in Drosophila. PLoS Biol. 2016;14:e1002455.
51. Billeter J-C, Wolfner MF. Chemical Cues that Guide Female Reproduction in Drosophila melanogaster. J Chem Ecol. 2018;44:750–69.
52. Akiba M, Sugimoto K, Aoki R, Murakami R, Miyashita T, Hashimoto R, et al. Dopamine modulates the optomotor response to unreliable visual stimuli in Drosophila melanogaster. Eur J of Neuroscience. 2020;51:822–39.
53. Masek P, Worden K, Aso Y, Rubin GM, Keene AC. A Dopamine-Modulated Neural Circuit Regulating Aversive Taste Memory in Drosophila. Current Biology. 2015;25:1535–41.
54. Bang S, Hyun S, Hong S-T, Kang J, Jeong K, Park J-J, et al. Dopamine Signalling in Mushroom Bodies Regulates Temperature-Preference Behaviour in Drosophila. PLoS Genet. 2011;7:e1001346.
55. Yao Z, Scott K. Serotonergic neurons translate taste detection into internal nutrient regulation. Neuron. 2022;110:1036-1050.e7.
56. Sitaraman D, Zars M, LaFerriere H, Chen Y-C, Sable-Smith A, Kitamoto T, et al. Serotonin is necessary for place memory in Drosophila. Proc Natl Acad Sci USA. 2008;105:5579–84.
57. Okray Z, Jacob PF, Stern C, Desmond K, Otto N, Talbot CB, et al. Multisensory learning binds neurons into a cross-modal memory engram. Nature. 2023;617:777–84.

58. Ghosh DD, Nitabach MN, Zhang Y, Harris G. Multisensory integration in C. elegans. Current Opinion in Neurobiology. 2017;43:110–8.
59. Metaxakis A, Petratou D, Tavernarakis N. Multimodal sensory processing in Caenorhabditis elegans. Open Biol. 2018 Jun;8(6):180049.
60. Hirokawa J, Bosch M, Sakata S, Sakurai Y, Yamamori T. Functional role of the secondary visual cortex in multisensory facilitation in rats. Neuroscience. 2008;153:1402–17.
61. Wallace MarkT, Meredith MA, Stein BarryE. Integration of multiple sensory modalities in cat cortex. Exp Brain Res. 1992;91.
62. Cappe C, Murray MM, Barone P, Rouiller EM. Multisensory Facilitation of Behavior in Monkeys: Effects of Stimulus Intensity. J Cogn Neurosci. 2010 Dec;22(12):2850-63.