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Closing the loop between neurobiology and flight behavior in *Drosophila*

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Fruit flies alter flight direction by generating rapid stereotyped turns called saccades. Using a combination of tethered and free-flight methods, both the aerodynamic mechanisms and the sensory triggers for saccades have been investigated. The results indicate that saccades are elicited by visual expansion, and are brought about by remarkably subtle changes in wing motion. Mechanosensory feedback from the fly's 'gyroscope' complements visual cues to terminate saccades, as well as to stabilize forward flight. Olfactory stimuli elicit tonic increases in wingbeat amplitude and frequency but do not alter the time course or magnitude of visual reflexes.

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Abbreviations

L–R left minus right
WBA wingbeat amplitude

Introduction

If seeing is believing, then, even by casual observation, flight in insects ranks among the most complex and demanding behaviors exhibited by animals. Flies in particular occupy the pantheon of nature's aviators [1] — they hover and maneuver in virtually any direction, maintaining equilibrium within turbulent conditions, track sparse odor plumes over vast distances, and fly so fast that their motion appears to most animals as an annoying blur. For example, houseflies can change course within 30 ms after visual displacement of a pursuit object [2]. Studying the extreme performance of fly flight offers insight into the general neural processes by which sensory signals are encoded, integrated and transformed into motor commands for complex behavior. Multiple feedback loops reverberate between different sensory mod-

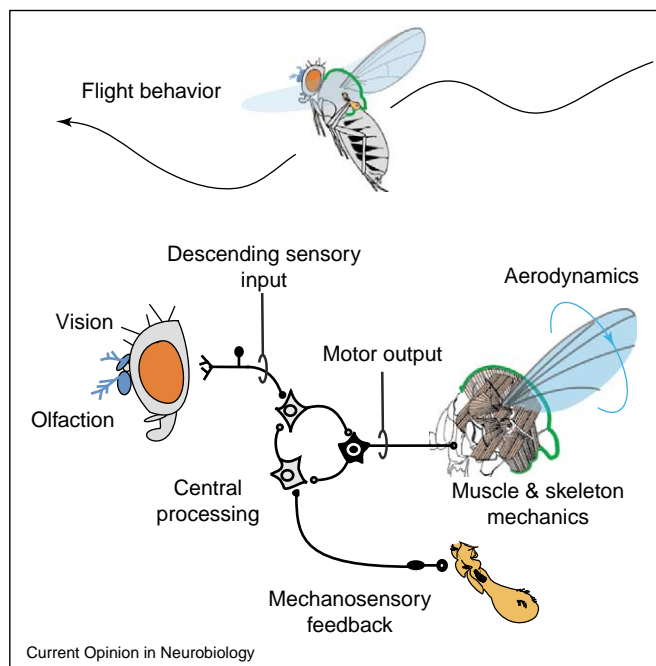
alities and their efferent control systems [3–5]. Therefore, when considering the neurobiology of flight behavior, it is impossible to disentangle the properties of sensory–motor control circuits from the aerodynamics of flapping, the biomechanics of the wing hinge, and the physiology of flight muscles (Figure 1). In this review, we describe a systems analysis of the aerodynamics, musculoskeletal mechanics and multisensory fusion that mediates a stereotyped flight maneuver. The quantitative behavioral analyses of this integrative approach predict specific structure–function relationships within the nervous system and thus pave the way for molecular-genetic and electrophysiological studies.

Aerodynamics and musculoskeletal mechanics

When searching for food, fruit flies explore their landscape using a series of straight flight paths punctuated by rapid yaw turns called saccades. During each saccade, the animal changes heading by 90° over a period of ~50 ms, corresponding to peak angular velocity exceeding 1000 degrees per second (Figure 2a; [6,7]). Current research programs combining dynamically scaled flapping robots, fluid flow visualization and computational simulations have provided an ever-clearer picture of the aerodynamic mechanisms by which insects stay aloft [8–10]. With this background, it is now more fruitful to examine the neural control of steering maneuvers such as saccades. A recent study used high-speed videography to capture the wing and body motions of free-flying *Drosophila*, then replayed the kinematics on a dynamically scaled robotic model to measure directly the aerodynamic forces [11*]. The wing kinematics during a saccade are remarkably similar to those during straight flight, showing changes only in the amplitude and orientation of the stroke. However, force measurements from the robot show that such subtle changes nevertheless produce enough yaw torque to rotate the body through a saccade (Figure 2b). These results indicate that during saccades, the motor system must exert very precise control over wing motions because small kinematic changes produce large aerodynamic results.

The flight musculature of flies is composed of two structurally, functionally and physiologically segregated groups. One group, the large power muscles, elevates and depresses the wings bilaterally, generating the mechanical power necessary keep the animal aloft. The other group, the small steering muscles, differentially alters the path and orientation of each wing during the stroke (Figure 2c; [12]). The power muscles exhibit a

Figure 1



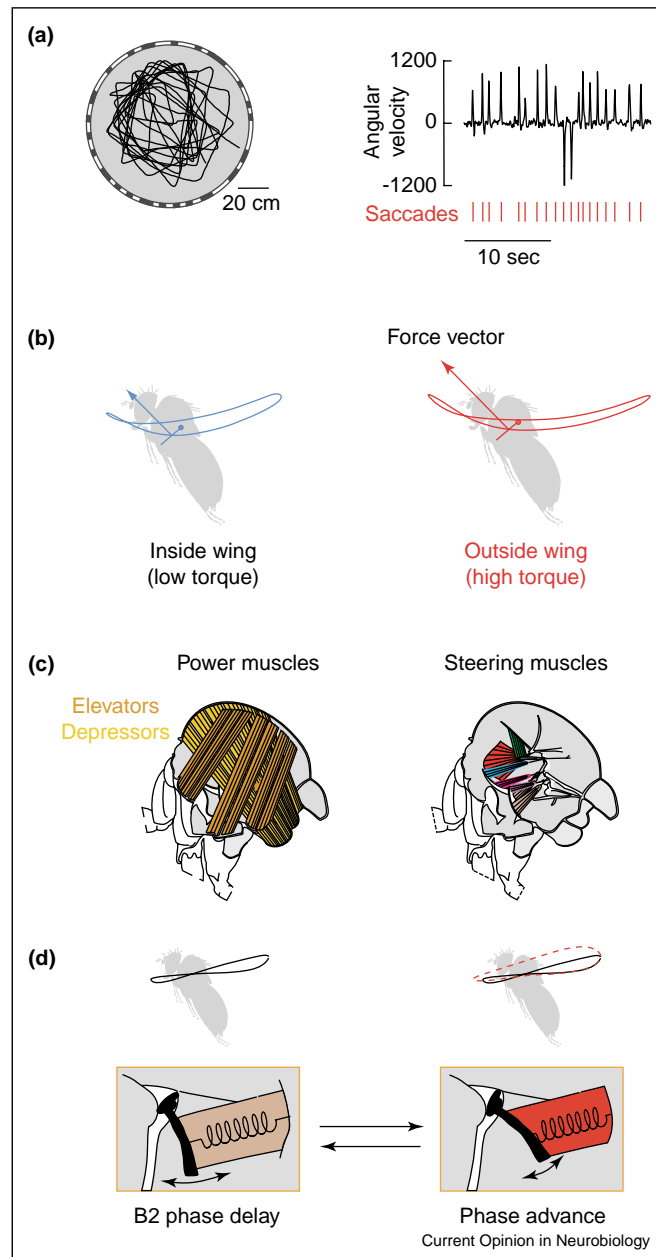
Schematic representation of the major flight control systems in *Drosophila* in which single cells represent the hypothetical flow of information within networks of sensory, motor, and interneurons. Visual and olfactory signals are encoded within the brain. Whereas the cellular mechanisms within primary sensory pathways have been extensively explored (e.g. [31**,37**]), the system of descending premotor interneurons that carries sensory feedback to the motor centers of the thorax is poorly understood. A mere dozen or so motor neurons control the complex repertoire of wing kinematics and aerodynamics necessary to keep the animal aloft and control flight maneuvers. To understand fully the operation of any one neural component within the cascade requires an integrative analysis of the system as a whole.

remarkable biophysical specialization that enables them to generate elevated power at high wingbeat frequency. Rather than being activated directly by presynaptic motor input, as in conventional twitch fibers, they are activated by stretch and deactivated by shortening [13]. Furthermore, because they are arranged in two antagonistic groups, contraction in one group results in stretch-activated contraction of the other after a short delay, giving rise to a mechanical resonance that oscillates the wings up and down at high frequency [14]. Owing to these biophysical specializations, a single presynaptic action potential results in a series of contraction cycles, and the power muscles are therefore described as asynchronous with respect to motor input [14]. The power muscles are not, however, entirely uncoupled from motor neuron input. A tonic elevation in firing frequency results in increased wingbeat amplitude and frequency but the changes occur over a time-scale of about 1 second [15], which is far too slow to coordinate rapid flight maneuvers. This task falls to the steering muscles that insert directly onto the wing hinge and are activated by neural input in the conventional one-to-one fashion [16]. Producing very little force themselves, these tiny muscles form an elaborate transmission system that regulates the means by which mechanical energy from the power muscles is trans-

formed into wing motion. Because *Drosophila* wings beat in excess of 200 Hz, a steering muscle motor neuron can only fire a single action potential within any given wing stroke. Thus, the most important control parameters for this muscle group are whether a given muscle fires within each stroke cycle [17] and the phase at which the spike occurs [18]. Furthermore, as a rule each steering muscle is innervated by only one motor neuron, forming a simple motor unit. Thus, the control scheme for the steering muscles stands in marked contrast to that of vertebrate skeletal muscle, in which motor unit recruitment and firing frequency regulate activation.

How can small changes in the firing phase of a small weak muscle produce the changes in wing motion necessary for a saccade? The conventional view of muscles as force-producing actuators has been recently expanded by comparative work showing that muscles can also act as springs, struts and even brakes [19]. Fly steering muscles behave like tunable springs; when tonically activated or phase shifted within the stroke cycle, changes in muscle stiffness alter the transmission properties of the wing hinge and subsequently modulate the path of the wing (Figure 2d; [20,21]). As a result of their role in coordinating saccades, the steering motor neurons represent a crucial bottleneck in the flight control circuit.

Figure 2



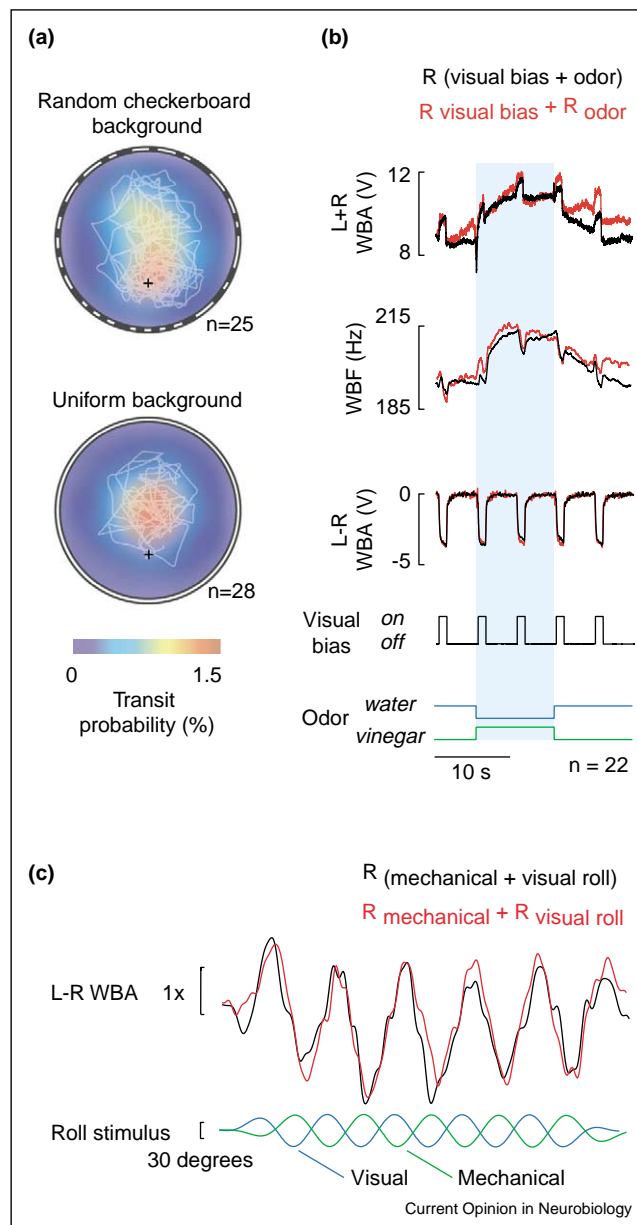
Control of rapid body saccades. **(a)** Left panel: a sample free flight trajectory, viewed from above, recorded from a fly exploring a cylindrical arena 1 meter in diameter and 0.6 meters high. The angular velocity of the fly's flight path is depicted in the right panel. Fruit fly flight is characterized by segments of straight flight (zero angular velocity) punctuated by rapid changes in angular velocity of the animal's heading, termed body saccades for their functional similarity to gaze stabilizing movements. **(b)** Aerodynamic forces mapped to saccade kinematics. The average path and resultant force vector are shown for each wing. The larger force vector on the outside wing propels the animal through the saccade. **(c)** The flight muscles are organized into two groups: powerful indirect muscles elevate and depress the wings, and tiny muscles insert directly on the wing base to steer each wing stroke. **(d)** Changes in recruitment and firing phase of a steering muscle alter the mechanical properties of the wing hinge to produce subtle changes in wing kinematics.

Spatial organization of visuomotor reflexes

The thoracic flight motor circuits are driven by massive convergence of sensory inputs, a large fraction of which descends from the visual processing centers of the brain. By tracking animals within a fixed visual panorama (e.g.

Figures 2a,3a), reconstructions of the fly's-eye view can be used to estimate the spatial and temporal characteristics of visual motion experienced by freely moving animals [6,22]. One such analysis of free flight in *Drosophila* suggests that patterns of visual expansion trigger

Figure 3

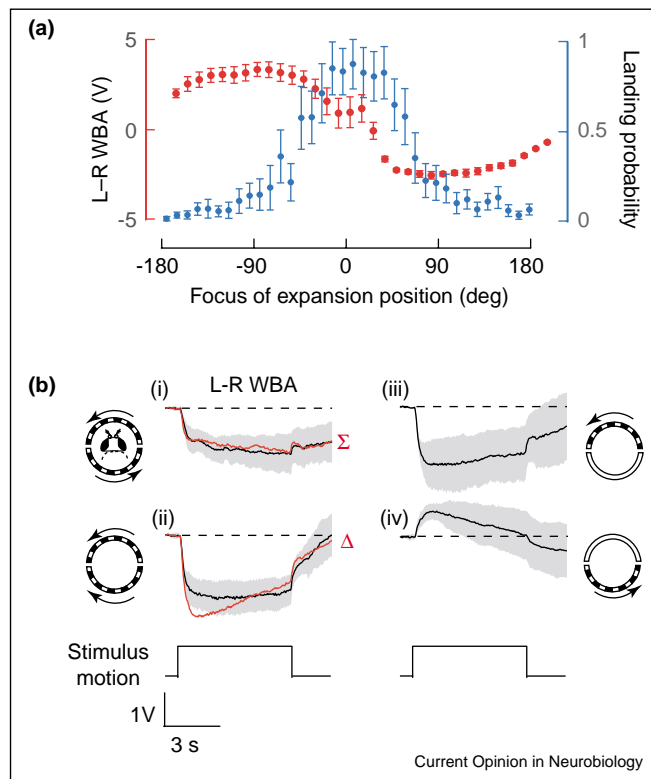


Multisensory control of flight behaviors. **(a)** Individual free-flight trajectories, viewed from above (translucent lines), are superimposed upon average instantaneous position histograms. The histograms are indicated in pseudocolor such that red shading indicates the position within the arena where flies are probably in transit. An attractive odor was placed under the floor at the position indicated by a black cross. When presented with uniform visual surroundings, animals fail to localize the odor source, indicated by the mismatch between the black cross and the maximum transit probability. **(b)** During tethered flight, motor responses reflect the linear superposition of multisensory inputs. Odor stimuli elicit tonic increases in total wingbeat amplitude (L+R WBA) and wingbeat frequency (WBF), whereas bias to the closed-loop control of visual expansion results in rapid turning responses indicated by changes in left-minus-right wingbeat amplitude (L-R WBA). The mathematical sum of independent responses (red) closely approximates responses to both stimuli presented concurrently (black). **(c)** A flight simulator mounted on a mechanical gimbal provides a means independently to track corrective steering reflexes in response to visual and mechanical rotation about the fly's roll axis. The sum of independent responses (red) closely approximates responses to both stimuli presented concurrently (black). L-R WBA responses are plotted as relative gain (scale bar 1x gain).

saccades away from approaching visual features [6]. Tethered fruit flies exhibit rapid fluctuations in yaw torque thought to be roughly analogous to free-flight saccades [23], and a rapidly expanding square reliably triggers a

saccade in the opposite direction — consistent with free-flight observations [24]. Varying the azimuthal position of the stimulus reveals a sinusoidal response curve that peaks 90 degrees from the fly's frontal field of view, in

Figure 4



Response to visual expansion in an electronic flight simulator. **(a)** Response maps generated by systematically varying the horizontal position of a rapidly expanding square. Collision avoidance maneuvers (red, left ordinate) are controlled independently from landing responses (blue, right ordinate). **(b)** Rotating a panoramic pattern of vertical stripes results in decreased left-minus-right (L-R) WBA, proportional to yaw torque, indicative of left turn (i). An expanding or contracting flow field, produced by reversing the direction of motion in the rear field of view, elicits a stronger turning response (ii). Rotating only the frontal field of view elicits a response comparable to full-field expansion (iii). Rotating only the rear field elicits a turning response in the direction opposite full-field rotation. The sum of half-field responses (iii+iv) approximates full-field responses (Σ), and the difference (iii-iv) approximates the saturated expansion response (Δ). Abbreviations: V, volts.

which an expansion centered on the right always evokes a turn to the left, and vice versa (Figure 4a, left ordinate). However, frontal expansion does not trigger a saccade but instead evokes a rapid extension of both front legs in a highly stereotyped landing reflex [25]. Unlike collision-avoidance responses, the probability of eliciting a landing response is maximal for a focus of expansion centered frontally [24] (Figure 4a, right ordinate). Thus, an expanding object can elicit both collision-avoidance saccades and landing responses but independent tuning curves suggest that the two motor reflexes are probably mediated by parallel neural pathways. In larger flies, the landing response is mediated by a specialized group of descending visual interneurons that have receptive fields tuned to frontal visual expansion [26]. There is likely to be an analogous cell group mediating collision-avoidance saccades but they have yet to be identified.

Between saccades, *Drosophila* tends to fly in a straight line. Theoretically, an animal could maintain a stable heading by minimizing panoramic image rotation. When

experimentally exposed to a rotating visual landscape, fruit flies, as well as many other animal taxa including primates, attempt to stabilize their gaze by turning in the same direction as the rotating panorama [27]. This behavioral response, the classic rotational optomotor equilibrium reflex [28], has often been used to analyze and predict structure-function relationships within the visual system of flies [29,30,31,32]. However, self-motion generates complex patterns of optic flow in six translational and rotational degrees of freedom [33] and little is known about the structure of visuomotor reflexes in response to compound patterns of optic flow.

To examine the visuomotor reflexes explicitly initiated by either panoramic image rotation or expansion, a pattern of vertical stripes was rotated horizontally around animals in the flight simulator [34]. When the whole pattern is rotated counterclockwise, flies turn left, as predicted by a rotational equilibrium model (Figure 4bi). An expanding pattern that generates no net rotation should elicit only a small turning response if the rotational

optomotor control system is linear. However, an expanding stimulus moving at the same contrast frequency results in an increased turning response — contradicting the simple rotational equilibrium model (Figure 4bii). Furthermore, reducing the spatial extent of the motion stimulus by moving only the front half of the display produces more robust turning responses than does the full-field stimulus (Figure 4biii). Most notably, motion restricted to the rear field of view results in a complete inversion of the turning response (Figure 4biv), with flies now turning in the opposite direction from that predicted by the classic optomotor model. Average full-field rotation responses are closely approximated by the mathematical sum of the opposite signed half-field responses (Figure 4bi Σ). Within the conditions of the flight simulator, expansion responses appear to be fully saturated because the mathematical difference between half-field responses is slightly larger in amplitude than the full field expansion (Figure 4bii Δ). Taken together, these results are consistent with a flight control system that maintains expansion equilibrium to both avoid collisions and minimize translatory side-slip.

Multisensory fusion

Drosophila has emerged as an important model for examining the mechanisms by which visual and olfactory signals are encoded and represented within the brain [35,36,37^{**}]. However, we know much less about the mechanisms by which the nervous system integrates or fuses input from multiple modalities and transforms it into motor output. Recent experiments in *Drosophila* suggest that visuo-olfactory integration is crucial for odor localization. Flies flown in an arena lined with a black and white random checkerboard pattern have little trouble localizing a visually camouflaged vial of apple cider vinegar. However, if presented with a spatially uniform panorama, flies fail to find the odor source and instead saccade back and forth near the center of the arena in a manner identical to the no-odor control (Figure 3a; [38^{*}]). Why does odor localization depend on visual feedback?

The detailed motor responses to multisensory input were recently explored by equipping a visual flight simulator with an odor delivery system. Animals were flown under closed-loop feedback conditions, such that attempts to turn (i.e. left-minus-right wingbeat amplitude [L–R WBA]) produced visual motion expected during unrestrained flight. Under these conditions, flies steered back and forth in an effort to suppress lateral image expansion (stimulus illustrated in Figure 4bii). Periodically, the animal was challenged with rightward bias added to the closed-loop control circuit. In response, flies rapidly compensated by steering left, away from the focus of expansion (Figure 3b, L–R WBA; [39]). The time course and magnitude of visual bias responses, characterized by rapid decreases in L–R WBA, do not change during stimulation with saturated vinegar vapor. Instead, flies

respond to odor with tonic increases in both total WBA and wingbeat frequency (Figure 3b). The mathematical sum of responses to the two stimuli presented in isolation — the formal test for linear superposition — suggests that there is no synergistic effect of combining visual and olfactory stimuli during flight (Figure 3b, red).

Multimodal superposition might be a common design feature of the fly flight-control system. Animals tethered within a flight simulator mounted on a mechanical gimbal exhibit robust compensatory turns in response to either rotation of the visual arena around a stationary fly or rotation of the fly within a stationary arena [40]. Mechanical equilibrium responses in flies are mediated by sensory organs called halteres, which independently encode body rotation along the roll, pitch and yaw axes [41]. Tethered animals that are free to rotate about the yaw axis exhibit shorter-duration saccades than do animals that are rigidly fixed, in which case haltere feedback is functionally disabled [42]. This result suggests that, whereas visual cues trigger saccades, haltere feedback is probably involved in terminating them. Although the visual system of flies ranks among the fastest ever studied [43,44], it is slow in contrast to haltere feedback [45], which is fast enough to entrain the firing phase of steering muscle motor neurons on a cycle-by-cycle basis [46]. Mechanical equilibrium responses continue to operate at rotational velocities exceeding 800 degrees per second, whereas visual responses are attenuated beyond 200 degrees per second. The frequency fractionation of the two systems effectively expands the dynamic range over which a fruit fly can counteract body rotation to maintain a straight heading. At intermediate speeds, the mathematical sum of responses to visual and mechanosensory roll is virtually identical to that evoked by presenting the two stimuli concurrently (Figure 3c). Thus, in the same way as in visual- and olfactory-mediated motor responses, visual and mechanosensory motor output is characterized by linear superposition of sensory inputs. These results suggest that multisensory input is either processed by separate parallel pre-motor pathways or multimodal interneurons are able to keep sensory information functionally segregated among independent channels.

Conclusions

An integrative systems approach linking aerodynamics, musculoskeletal mechanics and neurobiology has framed a working hypothesis for the control and dynamics of flight maneuvers in flies. As a fly explores its sensory landscape seeking the source of attractive odors, visual and mechanosensory feedback counteracts rotations of the body to maintain a straight flight path. Periodically, centers of image expansion generated by approaching objects or sideways body translation are relayed from the brain along specialized descending premotor networks to trigger rapid all-or-none body saccades. Once initiated, mechanosensory feedback from the halteres

probably serves to terminate the saccade, limiting the body rotation to 90 degrees. The aerodynamic torque to generate a saccade is produced by very rapid and subtle changes in wing kinematics, which are in turn coordinated by small shifts in the firing phase of steering muscles. Encountering an odor plume results in a forward surge, mediated by slow bilateral increases in WBA and wing-beat frequency, and is probably controlled by increased neural drive to the indirect power muscles. Whereas visual feedback is required for successful odor navigation, olfactory cues do not alter the sensitivity of visuomotor reflexes. Instead, visual-, olfactory- and mechanosensory-mediated motor responses are superimposed to produce stable, robust and flexible flight behavior. These results present sensory fusion and sensorimotor integration in a behavioral context. The next challenge is to discover the cellular mechanisms by which the encoded representations of visual, olfactory and mechanosensory signals are decoded by the motor system. One crucial bottleneck is the network of premotor descending neurons that filter tonic sensory signals from higher visual and olfactory centers, integrate mechanosensory cues and somehow translate them all into the phase code of the motor system.

Update

The focus of a recent study by Tang *et al.* [47] is beyond the scope of this review. However the authors make use of similar methods to examine the mechanisms of visual memory during flight. They use an electronic flight simulator to train a tethered fly to avoid actively a negatively conditioned visual object by steering left and right. After a training period the authors reposition the object upward and test whether or not the animal continues to avoid the object even though it appears in a novel region of the eye. The results suggest that flies, similar to other animals including humans, are able to discriminate a learned visual feature regardless of where it appears in the visual field.

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