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Generation and Evolution of Neural Cell Types and Circuits: Insights from the *Drosophila* Visual System

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Abstract

The *Drosophila* visual system has become a premier model for probing how neural diversity is generated during development. Recent work has provided deeper insight into the elaborate mechanisms that control the range of types and numbers of neurons produced, which neurons survive, and how they interact. These processes drive visual function and influence behavioral preferences. Other studies are beginning to provide insight into how neuronal diversity evolved in insects by adding new cell types and modifying neural circuits. Some of the most powerful comparisons have been those made to the *Drosophila* visual system, where a deeper understanding of molecular mechanisms allows for the generation of hypotheses about the evolution of neural anatomy and function. The evolution of new neural types contributes additional complexity to the brain and poses intriguing questions about how new neurons interact with existing circuitry. We explore how such individual changes in a variety of species might play a role over evolutionary timescales. Lessons learned from the fly visual system apply to other neural systems, including the fly central brain, where decisions are made and memories are stored.

INTRODUCTION

The nervous system relies on precise patterns of connectivity among a vast array of distinct neural cell types for proper function. These cell types must first be specified at the appropriate time and place during development. Understanding how this great diversity of neural types is generated and how these neurons make connections to form a functional brain is one of the biggest challenges in biology today (1, 28, 93).

The specification of neural cell types and how they interconnect is largely encoded by the genome. Differences in neural function often reflect changes to how cell fate is specified and interpreted. Understanding neural development is therefore critical for understanding how the genome encodes neural function.

An experimental neural system with functional–behavioral outputs that can be robustly interrogated at the molecular and circuit level is the visual system of *Drosophila melanogaster*. The *Drosophila* visual system provides a tractable model for understanding such questions using arguably unparalleled genetic tools. The first part of this review examines how cell fate is specified during development of the *Drosophila* visual system, focusing on recent advances in our understanding of the generation of neural diversity. We describe how the intersection of where and when during neuronal specification explains much of the neural diversity observed. Newly developed tools, combined with an extensive existing body of research, have allowed researchers to make great headway in understanding the black box of visual system development in *Drosophila*—yet much is still not understood.

The second part of this review focuses on specific cases where neural types have been modified or have newly evolved to provide specific adaptive functions in the visual systems of a diverse range of insects displaying a wealth of evolutionary divergence. Despite high levels of conservation of visual system components across the insects, specific cases provide a glimpse into how a complex neural system might evolve and change, from the specification of cell types to the output of neural circuits. Using an abundance of detailed knowledge from *Drosophila*, one can compare the morphological differences among species and glean insight into the mechanisms underlying evolutionary divergence. This comparative approach allows the generation of targeted hypotheses: We can look not only for differences in morphology between species, but also for changes in the distribution of cell types produced and the genes these cells express. The development of new tools such as CRISPR/Cas9 is making it increasingly possible to test such hypotheses and evaluate developmental mechanisms directly in nonmodel species that exhibit interesting differences in function, morphology, or distribution of neural types. In the future, this approach will include direct manipulation of cell types and their properties to test hypotheses about the genetic basis of neural adaptation, as well as more sophisticated features such as how behaviors are genetically encoded. Examining the genetic and developmental basis of such differences has begun to provide key insights into how and why the brain functions as it does and is an exciting and active area of research.

A final section summarizes what is known about deeper evolutionary relationships between the different neural structures (neuropils) across different insect brains. As the distinct structures of additional neuropils arose via duplication or subdivision (125), divergences in cell-fate specification pathways likely contributed to additional neural diversity and function. We discuss research findings that suggest how each additional neuropil might contribute to visual processing. It has been suggested that the core set of transcription factors that define cell fate can be used to establish homology of cell type, if not evolutionary origin (5). We propose a strategy that uses tools in highly manipulable model systems such as *Drosophila* to identify these factors for key cell types, and which then uses these specifiers of identity as markers to evaluate the distribution of homologous cell types in species with different numbers of neuropils. This approach will help uncover the origins

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of these cell types in a common ancestor and provide insight into the mechanisms underlying deeper evolutionary divergences in neural systems.

DEVELOPMENT: GENERATION OF CELL-TYPE DIVERSITY

Cell fate is established during development using a combination of spatial and temporal cues. In the following sections, we highlight how the intersection of these cues can be used for the generation of cell-type diversity in the *Drosophila* visual system. Although there are many examples where spatially distributed factors are used to specify cell fate during development, temporal control of specification is often less well understood (75). One of the best examples of temporally dynamic cell-fate specification comes from the *Drosophila* retina.

The Retina

The adult *Drosophila* retina is patterned during larval development by the progression of a wave of differentiation across the eye imaginal disc (108), and this patterning is intimately linked with differentiation of the four deeper, distinct neuropils of the visual system: the lamina, the medulla, the lobula, and the lobula plate (**Figure 1*a–f***). Development of the retina has been reviewed in depth previously (79, 114). Here, we summarize retina development and structure before discussing advances in our understanding of the coordinated patterning of deeper layers (where there has been much recent progress). We go on to review how these insights relate to the addition of new photoreceptor types in the retina.

During the third larval instar (larval stage), a groove called the morphogenetic furrow sweeps progressively across the eye imaginal disc from posterior to anterior (108, 114). Cells anterior to the furrow are undifferentiated, whereas cells behind the furrow are recruited into regularly spaced clusters and become increasingly differentiated to form individual ommatidia (134, 148) (**Figure 1*a***). The progression of the furrow and the founding of individual ommatidia involve multiple signaling pathways: Hedgehog (Hh), Decapentaplegic (Dpp), and Epidermal growth factor (EGF) all play important roles (reviewed in 114). Notch lateral inhibition is used in specification of the R8 photoreceptor, the founding cell of each ommatidium (114). The R8 cell then plays a role in recruitment of pairs of all other photoreceptors through sequential use of the EGF receptor pathway: R2/5 are added first, then R3/4, then R1/6, and finally R7 (37, 114). Recruitment of the R7 photoreceptor is arguably one of the most heavily studied cell-fate specification events in biology (132). It was used in forward modifier genetic screens to identify and characterize many components of Sevenless (Sev) signaling and successfully identified nearly every component of what came to be known as the Ras/ERK pathway (8, 96, 113; reviewed in 79). R7 specification is still the subject of ongoing research and is of more recent evolutionary interest because the number of R7 photoreceptors has changed in species of insects to improve their color vision (38, 105) (see the section titled Two R7s Provide Added Diversity to the Retina).

In *Drosophila*, photoreceptors project their axons directly into the optic lobes and send output to the lamina and medulla (**Figure 1*b***), where it is processed and relayed to the lobula complex and central brain (33). During development, photoreceptors R1–6, also known as outer photoreceptors, target their axons to the lamina, producing short visual fibers, whereas R7 and R8 axons produce long visual fibers, continue through the lamina, and end in layers M6 (R7) and M3 (R8) of the medulla (25, 94). R1–6 express the broad-spectrum Rhodopsin Rh1 and are thought to be primarily involved in motion vision, whereas the inner photoreceptors R7 and R8 express wavelength-specific Rhodopsins and are used in making color comparisons (24, 111). Two subtypes of ommatidia are distributed stochastically across the retina (36). One subtype that expresses

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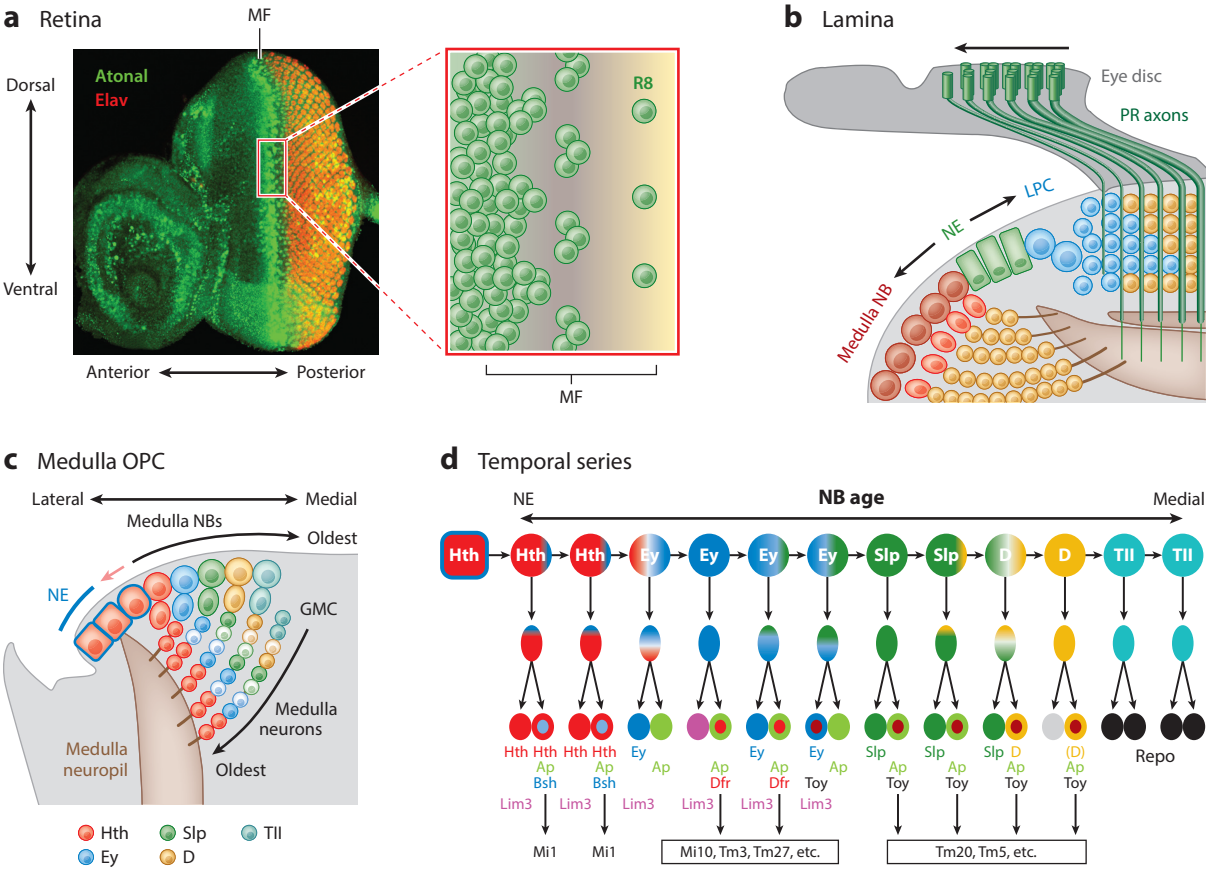

UV-sensitive Rh3 in R7 and blue-Rh5 in R8 represents approximately 65% of ommatidia, whereas a second subtype that expresses a distinct UV-Rh4 in R7 and green-Rh6 in R8 is present in approximately 35% of ommatidia (reviewed in 111). This probability-based, stochastic patterning is controlled by expression (or lack of expression) of the transcription factor Spineless in each R7 cell during development (66, 67, 142). The decision in R7 then modifies the fate of R8 via a combination of activin and bone morphogenetic protein signaling in order to produce the coordinated outcomes necessary for proper ommatidial function (24, 101, 139a). Removal of *spineless* causes the production of the Rh3/Rh5 subtype in all ommatidia, whereas its overexpression in all photoreceptors causes all ommatidia to express Rh4/Rh6 (142).

Initial patterning produces a very stereotyped and reproducible crystalline array of ommatidia, each with a complete complement of photoreceptors and accessory cell types, such as cone, pigment, and bristle cells (37, 108). Further patterning in late larval and early pupal stages produces a stochastic, random arrangement of the two ommatidial types, Rh3/Rh5 or Rh4/Rh6. (142). This stochastic patterning step provides additional diversity in cell types across the retina, allowing for comparisons between more wavelengths than would be allowed by a single ommatidial type. This diversity has continued to expand with the addition of a third stochastically distributed ommatidial type in butterflies (6, 105) (see the section titled Two R7s Provide Added Diversity to the Retina).

The Lamina

Development of the lamina is intimately coupled with development and patterning of the retina. The lamina and medulla are patterned from a crescent-shaped neuroepithelium called the outer proliferation center (OPC) (29, 61). During the third larval instar, as photoreceptors are progressively specified in the retina, fasciculated bundles of axons from the oldest, most posterior photoreceptors are the first to reach the site of the future lamina on the inner side of the OPC neuroepithelial crescent (**Figure 1*b***) (60, 114). This part of the neuroepithelium is progressively converted into lamina as more photoreceptor axons arrive and provide inductive signals necessary for lamina differentiation (60, 61). This process is tightly regulated by the photoreceptor axons. Hh is initially dispatched to signal lamina precursor cells to enter cell division and align along the length of the photoreceptor axons. Differentiation of these precursors into lamina cells has

Figure 1

Visual system development and patterning. (*a*) The cell types of the retina are specified during the third larval instar. An MF sweeps across the eye imaginal disc from posterior to anterior, leaving behind evenly distributed R8 PRs. Each R8 PR then begins a recruitment process that sequentially recruits the other seven PRs in *Drosophila* (reviewed in 114). (*b*) Lamina neurons are dynamically specified one row at a time via signals from incoming PR axons (60, 61). Little is known about how the five different lamina monopolar cell types are differentially specified using similar signals from PR axons. (*c*) In the OPC, medulla NBs are sequentially recruited from NE and first divide to produce GMCs, which then divide to produce neurons. Each NB produces a chain of progeny. Because they were specified first, the oldest neurons appear at the bottom (81). Hth, Ey, Slp, D, and Tll are sequential transcription factors. (*d*) Over time, NBs change their transcriptional profiles as they transition from one transcription factor to the next in a temporal series. Loss of Ey, Slp, or D prevents transition to the next factor in the series (82). These temporal transitions help to generate much of the neural diversity of the medulla. (*e*) Input from regional factors across the OPC produces additional diversity (31). Together, the temporal series plus regionalization produce the highly diverse types of neurons that make up the adult medulla. (*f*) Specific cell types have recently been shown to form the basis of elementary motion detectors that relay information to the four layers of the lobula plate (*yellow*) (26, 29, 64, 65, 112). ON- (*blue*) and OFF- (*green*) edge detection relies on different pathways and cell types. (*g*) T4 and T5 neurons are ON- and OFF- pathway specific as well as directionally selective in the lobula plate. Shown here is R42F06–GAL4 driving CD8:GFP. It has been proposed that these neurons may be some of the most highly evolutionarily conserved cell types of the visual system (118). Abbreviations: GMC, ganglion mother cell; LPC, lamina precursor cell; MF, morphogenetic furrow; NB, neuroblast; NE, neuroepithelium; OPC, outer proliferation center; PR, photoreceptor. Panel *a* modified with permission from Reference 45, panels *c* and *d* from Reference 82, panel *e* from Reference 31, and panel *f* from Reference 13.

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recently been shown to involve a relay where photoreceptors first signal to glial cells using the EGF ligand Spitz, and glial cells in turn express insulin-like peptides to induce differentiation (31a, 60–62). This leads to the production of five different lamina monopolar cells (LMCs) (L1–L5) in each of the cartridges innervated by photoreceptors. Finally, besides inducing differentiation of LMCs, the photoreceptor axons seem to be general conductors of lamina development by also guiding the migration and differentiation of glial cells (102, 103, 147).

The end product of this process is five distinct layers of LMCs, each providing individual function (91, 136). L1 and L2 are necessary for motion detection: Silencing both L1 and L2 leads to complete elimination of the fly's responses to motion (136). These neurons provide the first input to downstream motion circuits that form the elementary motion detectors. L1, together with L3, provides input to the circuit that detects bright edges (ON pathway), whereas L2 feeds into the motion detector for dark edges (OFF pathway) (64, 69, 119, 136). The roles of the other LMCs had not been appreciated until recently, as they seem to be more subtle. L4 receives synaptic input from L2 and participates in the OFF pathway; silencing L4 results in a phenotype similar to that of L2 and renders the flies insensitive to moving dark edges (136). L3 seems to play a parallel role to L1 and L2, and it is the primary input for low frequency stimuli, i.e., slow motion stimuli (119, 136). The role of L5 remains a mystery.

Although the lamina is patterned in a temporally dynamic way, it is composed of just five repeated individual cell types. Despite this limited diversity, circuit-level interactions provide the complexity necessary for proper motion processing. Because of the relative simplicity of this limited set of cells, the lamina has been more tractable, historically, than the much more complex and diverse medulla.

Lamina function is modulated by seven other cell types that also innervate the lamina, though they do not originate from the lamina part of the OPC neuroepithelium and their cell bodies are not in the lamina cortex. Three columnar neurons, T1, C2, and C3, provide feedback information from the medulla (32, 136). The other four are multicolumnar neurons. The function of Lai (lamina-intrinsic) neurons is not yet known. Lat (lamina-tangential) neurons, according to their structure and arborizations, seem to be involved in relaying feedback to the lamina from the circadian circuit (136). Finally, Lawf1 and Lawf2 (lamina wide-field) neurons provide broad field feedback from the medulla (23, 136). These seven neural types are derived from different sources than the LMCs and emerge from the medulla part of the OPC, the inner proliferation center (IPC), or neuroblasts in the central brain, making the lamina a composite of cells that arise from spatially independent precursors.

The Medulla

The medulla is the largest neuropil and is composed of approximately 40,000 cells belonging to a diverse array of cell types (33, 41). The medulla processes color and motion information, receiving direct input from the R7 and R8 color photoreceptors as well as input from the LMCs (112). Photoreceptors and LMCs project to individual medulla columns that correspond to the approximately 800 ommatidia and 800 associated lamina cartridges that lie above. Each column processes information from one portion of the visual field (95) and provides a continuation of retinotopic information through the neuropil layers.

At least 80 neuronal types contribute to the connections in each column, and these neurons can be categorized into two classes: Unicolumnar neurons arborize primarily in one medulla column, whereas multicolumnar neurons send their arbors over multiple columns (33, 95, 129, 131). Unicolumnar neurons are therefore present at a 1:1 ratio with the number of medulla columns, which are in turn found at a 1:1 ratio with the number of ommatidia (of which there are approximately 800). There are fewer multicolumnar neurons, but these presumably average inputs

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from neurons over larger receptor fields. One of the most interesting features of the medulla has turned out to be the dynamic way in which this diversity of neural types is generated.

Temporal series. Recent work has significantly advanced our understanding of how neural diversity is generated in the *Drosophila* medulla. The external morphology of the optic lobes during development had long been well characterized (90), and the morphology of over 70 medulla cell types was detailed in a now-classic paper from Fischbach & Dittrich (33). New studies have shown that most if not all of this diversity is produced by neuroblasts that progressively express a sequence of different transcription factors over time in a temporal series (81, 128).

Temporal patterning of neuroblasts was first characterized in the *Drosophila* ventral nerve cord in work from the Doe and Odenwald laboratories in the late 1990s and early 2000s (63, 68; reviewed in 75). These neuroblasts divide asymmetrically to produce ganglion mother cells (GMCs), which then divide to produce neurons. A series of transcription factors is expressed one after the other in the same neuroblast over time, and progeny resulting from neuroblast divisions within each temporal window give rise to different neural types from one window to the next. In the ventral nerve cord, this series progresses through the transcription factors Hb → Kr → Pdm → Cas → Grh (15, 48, 63).

Fifteen years later, a new temporal series was discovered in the *Drosophila* medulla, and it uses the same general principle but an entirely different set of temporal transcription factors (82, 128). The OPC gives rise to medulla neuroblasts on the outer side of the neuroepithelial crescent. These divide asymmetrically to produce GMCs, which then divide to produce neurons in growing chains of cells in which position reflects birth order (**Figure 1*c***). Five transcription factors are expressed in each neuroblast in series: Hth → Ey → Slp → D → Tll. Loss of expression of Ey, Slp, or D stops the progression of the temporal series, causing the preceding temporal window to be extended, indicating that these factors are directly necessary for temporal progression from one state to the next. Distinct neural cell types are generated by neuroblasts during each temporal window (82) (**Figure 1*d***). Dividing GMCs each produce two different types of neurons in the main region of the OPC using Notch-based asymmetric division (82). In theory, these mechanisms could explain how at least 20 neuronal types are produced by each neuroblast (**Figure 1*d***). Additional mechanisms were required to explain the full diversity of medulla cell types observed (approximately 80), and another recent study (31) has found that some of this additional diversity stems from reginal identity.

Regional identity. The production of additional cell-type diversity in the medulla takes advantage of regionalized positional information (31). Although all neuroblasts in the OPC progress through the same temporal series, spatially distributed factors modify the types of neurons that are produced in each of at least eight distinct regions along the crescent (**Figure 1*e***). The two sides (dorsal and ventral) of the crescent express Vsx1, Optix, Dpp, and Wg in mirror symmetry (from the center to the tips), whereas Hh is expressed only in the ventral half. It appears that neural types that are present at a 1:1 ratio with the number of columns in the medulla (unicolumnar neurons) are produced in all compartments independently of spatial input (31). Multicolumnar neurons that span multiple columns and that are fewer in number are produced in spatially restricted domains along the crescent of the OPC, i.e., from fewer neuroblasts. These neurons innervate the entire retinotopic map and later move to become distributed across the medulla (31). The combination of temporal and spatial cues thus explains much of the diversity of cell types observed in the medulla. Ongoing efforts are aimed at connecting specific progenitors in *Drosophila* larval stages to each of the types of previously characterized adult neurons.

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Deeper Optic Lobe Layers: The Lobula and Lobula Plate

Motion perception is the best-studied visual modality in the fly, and its neuronal implementation is one of the best understood neural systems in any organism (for an in-depth review see 10, 14). Motion perception is critical for multiple behaviors, such as the integration of the fly's own movements, predator avoidance, and—in several species—prey capture and mating.

Wide-field motion information is computed by a precise neuronal circuit of parallel ON and OFF pathways (26, 30, 64, 65, 112) (**Figure 1*f***). Each pathway relies on a specific set of lamina and medulla neurons that feed into T4 (ON) and T5 (OFF) cells (2, 116, 117, 129, 130) (**Figure 1*g***). Four subtypes of T4 and T5 neurons, each tuned to one of the four cardinal directions of motion (84), project to one of the four layers of the lobula plate (shown in **Figure 1*f***), where they are presynaptic to the output neurons of the motion pathway, the lobula plate tangential cells (86, 115). Importantly, elegant studies have shown that directional tuning is first observed in T4 and T5 neurons (34, 84), whereas none of the neurons upstream of T4 and T5 are direction-selective (2, 9, 89, 116, 127).

The lobula plate is mostly innervated by neurons that are part of the motion circuit: T4/T5 neurons, lobula plate tangential cells (LPTCs), and, as discovered more recently, the lobula plate-intrinsic (LPi) interneurons (87). The lobula plate is thus rightfully known as the cockpit of the fly (14). Therefore, understanding the evolution of this neuropil can generate insights into how motion processing evolved. The T4/T5 neurons are produced by a collection of neural progenitors that originate from three adjacent neuroepithelial domains of the IPC; two domains marked by the expression of *dpp*; and, between these, a domain marked by the expression of *brk*, a *dpp* target and a repressor of the *dpp* pathway (3). Starting at the late larval stage, and in parallel with the conversion of the OPC neuroepithelial cells into neuroblasts, the proximal IPC neuroepithelium progressively produces progenitors which migrate distally to form a second neurogenic domain, the distal IPC, a symmetric horseshoe adjacent to the lamina and OPC crescents (3). Progenitors in the distal IPC initially produce the T2/T3 and C2/C3 distal neurons and then give rise to T4 and T5 neurons (3, 100). The role of Dpp and Brk for the development and specification of the neuroepithelial domains is not known, nor is the contribution of each domain to the full complement of T4/T5 neurons or the exact lineage relationship between T4 and T5 subtypes. Understanding the neurogenesis of T4 and T5 neurons and how their subtype identities relate to the different IPC neuroepithelium domains will allow us to characterize the development of ON and OFF pathways and each of the direction-selective circuits.

EVOLUTION OF CELL-TYPE DIVERSITY

A major focus of the field of evolutionary developmental biology, or evo–devo, has been to understand the genetic basis of morphological evolution (21). Now-classic evo–devo studies suggest that diversity in animal body plans is generated by variation of a limited number of developmental themes and by changes in the expression of a relatively small core set of developmental genes (reviewed in 21). Although the genetic basis of neural evolution remains less well understood, studies are beginning to suggest that a similarly limited number of core, conserved mechanisms play important roles in both the generation of neural diversity and the evolution of new neural types.

In this second part of this review, we discuss specific examples of cell-fate evolution from insect visual systems. We have selected examples that have proven (or may prove) to be especially tractable cases for determining the underlying molecular basis of modifications to neural patterning mechanisms. Such changes are particularly interesting when they have been made to allow the animal to adapt to specific visual requirements that are imposed by the environment or

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specific behaviors. We focus especially on cases where our understanding of the *Drosophila* visual system provides clues, insight, and testable hypotheses. Although there is a long history of studies providing excellent examples of the evolution of new neural types, using, for example, the tools of comparative embryology, ultrastructure research, electrophysiology, and neuroethology, the genetic basis of these differences has just begun to be explored. Adding molecular and genetic tools to more traditional comparative approaches will be important for understanding how the brain evolves.

Evolution of Retinal Pathways

Although insect retinas vary in size and physical properties (44), the number and types of cells within each ommatidium is highly conserved across many insect groups (143). Yet several examples of specific modifications have been studied. A first example involves the specialization of an R7 photoreceptor for novel function in a specific part of the eye in male flies. Another example involves the evolution of a second R7 photoreceptor per ommatidium in butterflies and provides an example of how neural diversity can be expanded for added functionality.

The Love Spot

In many species in the Diptera, and in some other insect species such as in the Ephemeroptera, male eyes look externally very different from their female counterparts (27, 104, 138, 150). Such differences are often correlated with female-chasing behavior. Perhaps the most obvious difference is that the eyes develop closer together, providing a more continuous visual surface, and often become holoptic (see **Figure 2*a***) (58, 138, 150). Ommatidia in the dorsal–frontal region are also often enlarged to provide higher sensitivity by collecting more photons. This change in size would come with a reduction in resolution (fewer ommatidia means viewing fewer points in space) except that concomitant changes in eye curvature, interommatidial angles, and acceptance angles instead compensate or even increase resolution (44, 80, 138). Decreasing the acceptance angle allows the light-gathering capacity of a given photoreceptor to focus on a smaller region of the sky, again increasing sensitivity. Each of these changes seems to adapt the male eye for a specific function: picking out and pursuing small, distant females against the uniform background of the sky. This specialization of the male dorsal–frontal eye is found in over fifteen families in the Diptera and has come to be known as the Love Spot (104).

The Love Spot has additional specialization at the photoreceptor and cell-fate levels. It was first noticed over 30 years ago that R7 photoreceptors in this region in *Musca domestica* produce the same filtering pigment as outer photoreceptors and not the stochastic distribution of pale (empty) or yellow pigmentation of normal R7s (35) (**Figure 2*b***). Electrophysiological recordings identified a broad-spectrum response from these R7 cells, similar to outer photoreceptors that express Rh1 (50–52, 58). Backfilling the recorded cells with dye showed that the axons of these photoreceptors stop short in the lamina, like outer photoreceptors normally do (52) (**Figure 2*c***). This provided evidence of at least partial conversion of Love Spot R7s from the color–inner photoreceptor fate toward the outer photoreceptor fate and suggested that this one additional outer-like photoreceptor provides input to motion detection. This must come at the expense of color vision, as R8 is no longer able to make comparisons with input from R7 in the medulla. Interestingly, *Musca* appears to have made further changes by modifying the connectivity to LMCs in the service of spotting and tracking females. As described above, L1 and L3 contribute to the ON pathway in motion detection, whereas L2 and L3 contribute to the OFF pathway (136) (**Figure 1*g***). Hardie (49) showed that converted Love Spot R7s of *Musca* specifically connect to L2 and L3 but

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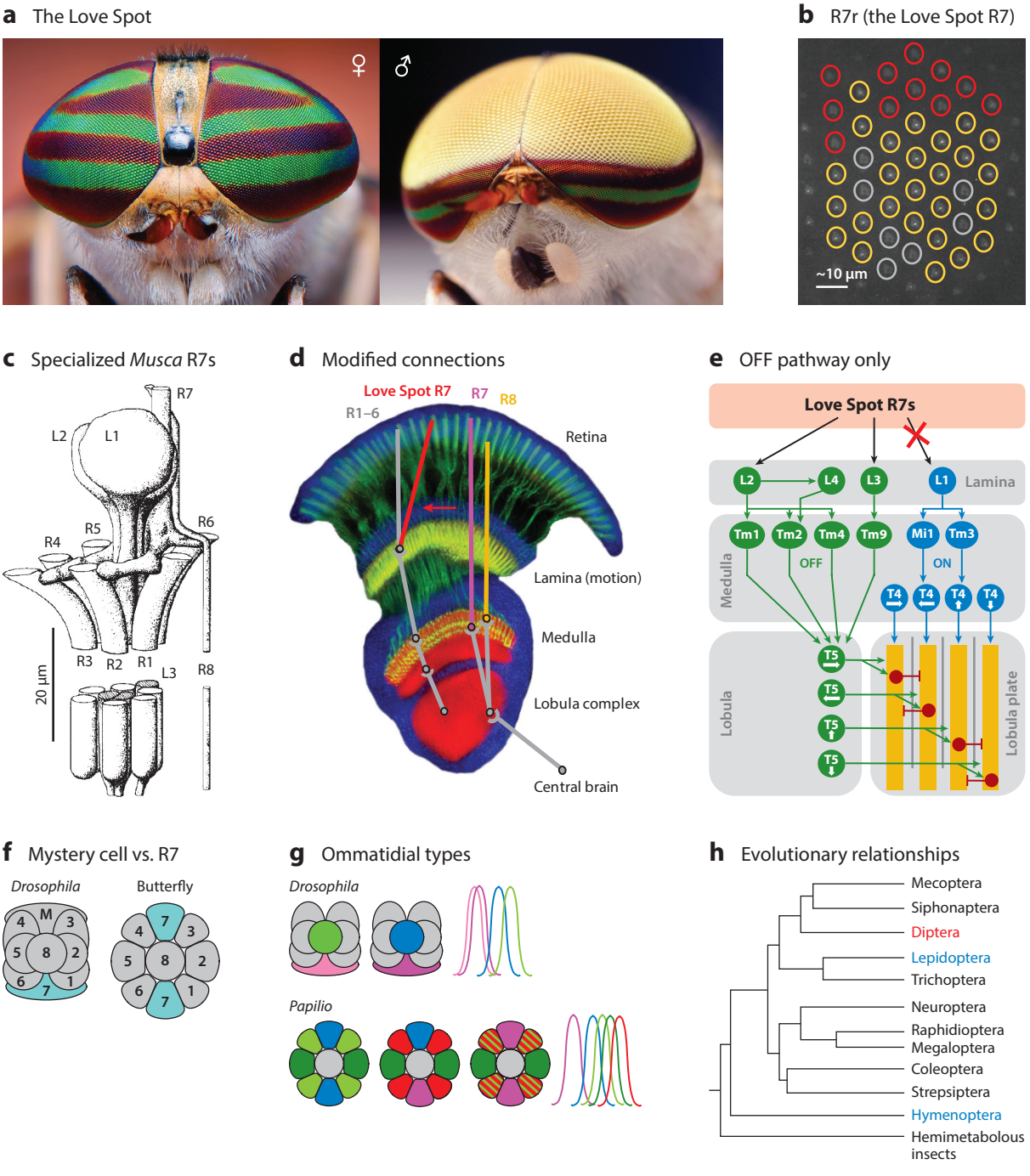

not to L1. This suggests that these photoreceptors provide input only into the OFF pathway as opposed to the ON pathway (**Figure 2*e***), consistent with the idea that these cells are used for the detection of small dark objects on a bright background (OFF). This suggests that Love Spot R7s represent a novel class of photoreceptors that are specialized for the detection of dark targets and no longer contribute fully to color vision or to global motion in this part of the male retina. It is unknown whether all species with Love Spot–like features have axons that stop short in the lamina (i.e., that convert from long visual fibers to short visual fibers), or if Love Spots in other families evolved independently, perhaps via modifying different underlying developmental mechanisms.

Two R7s Provide Added Diversity to the Retina

The first step in the evolution of additional complexity may not require the divergence of a novel, more specialized cell type from an existing one. Many species in the Lepidoptera have nine photoreceptors instead of the eight found in flies, beetles, and most other insects (38, 105). This additional photoreceptor was found to be a second R7-type photoreceptor (105). This photoreceptor is recruited during development in the same position as a cell known as the mystery cell in *Drosophila* (132), and it has been suggested that Lepidoptera retain the mystery cell as an additional R7-type photoreceptor (105) (**Figure 2*f***). Retention of this additional R7 cell has an unexpected outcome: Because R7 photoreceptors control the stochastic distribution of ommatidial types, as discussed above, the addition of a second R7 allowed for the evolution of a third stochastically distributed ommatidial type (**Figure 2*g***) (105). Instead of an ON/OFF binary decision to express Spineless in the unique *Drosophila* R7 cell, *Papilio* butterflies, for example, make two independent ON/OFF decisions in each R7 cell, leading to ON/ON, ON/OFF, OFF/ON, and OFF/OFF combinations, with ON/OFF and OFF/ON resulting in functionally equivalent ommatidia. This decision has been coupled to the type of Rhodopsin and pigments expressed in neighboring photoreceptors that are homologous to *Drosophila* R1/6 and R3/4 photoreceptors (105). In the swallowtail butterfly *Papilio xuthus*, these outer-like photoreceptors also express a

Figure 2

Evolution of new neural types in the visual system. (*a*) The eyes of female (*left*) and male (*right*) *Tabanus* in the family Tabanidae (the horse and deer flies) are noticeably different. The Love Spot is a specialized region of the male dorsofrontal eye found in many species of Diptera and is used for detecting and chasing females (104). (*b*) Some cell types in the Love Spot have become specialized for these functions. In *Musca domestica*, female eyes and ventral male eyes produce yellow fluorescence under blue illumination in a stochastic subset of inner R7 photoreceptors (*yellow* versus *gray circles*) (36, 51). Male retinas have specialized ommatidia in the dorsofrontal region that instead produce the same reddish fluorescence of outer, motion-sensitive photoreceptors—initially termed R7r (*red circles*) (36). (*c*) The dye-filling of photoreceptors after electrophysiological recordings was used to characterize the morphology of *Musca* Love Spot R7 photoreceptors (49, 52). They end in a foot in the lamina that is distinct from both inner and outer photoreceptors (49). (*d*) The Love Spot R7s change connectivity. Normal R7s (*purple line*) project to the medulla; the Love Spot R7s (*red line*) instead project to the lamina, like R1–6 (52). (*e*) Electron microscopy reconstruction of the Love Spot R7 terminals shows that they connect primarily to L2 and L3 and not to L1 (49). This suggests that they feed into the OFF pathway (*green*) and not ON (*blue*), which may reflect their function. (*f*) Butterflies have nine photoreceptors instead of the eight found in flies and most insects (other than Hymenoptera) (6, 105). This additional photoreceptor has been shown to be of the R7 type and is recruited in the same position as the mystery cell (M) of *Drosophila*, which transiently appears and disappears (105). (*g*) The additional R7 photoreceptor allows for the production of three stochastic outcomes in butterflies instead of the two found in *Drosophila*. This third stochastic type has been used to specifically deploy a newly evolved red-sensitive Rhodopsin in *Papilio* butterflies. (*h*) Evolutionary tree showing the relationships between insect orders, including the Lepidoptera and Hymenoptera (*blue*). Panel *a* modified with permission from Reference 104, panel *b* from References 36 and 51, panel *c* from Reference 49, panel *d* from Reference 146, panel *e* from Reference 13, panel *f* from Reference 133, and panel *h* from Reference 145.

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red-sensitive Rhodopsin in just one of the three ommatidial types (see the wavelength overview in **Figure 2*g***) (6). Therefore, the evolution of a second R7-like cell immediately produced three types of stochastic outcomes, and this additional positional information was later coopted for the expression of more specialized Rhodopsins. This increase in ommatidial diversity allows for additional color comparisons and for additional ranges of wavelengths to be perceived, and indeed butterflies have a well-known ability to excel at color discrimination when choosing flowers and mates (12, 22, 70, 72–74). These changes must also have implications for circuit-level evolution (see the section titled Evolution of Neural Circuits).

Another group of insects also has nine photoreceptors and three ommatidial types. The Hymenoptera—including ants, wasps, and bees—also appear to have an additional R7-type photoreceptor, though this has not yet been investigated directly using molecular markers or functional experiments as in butterflies (38, 105, 107, 121, 137). Given the distant phylogenetic position of Hymenoptera versus Lepidoptera (e.g., 145) (**Figure 2*b***), it is interesting to consider whether Hymenoptera independently evolved a second R7 photoreceptor or whether multiple groups have lost it. This question will likely not be answered without further investigation of intermediate groups such as the Trichoptera and outgroups of the holometabolous (metamorphosing) insects.

Additional examples of retina evolution may involve the addition of new photoreceptor types. Some insect species such as mosquitoes and water striders exhibit specialized ventral regions or stripes that may function in water detection using polarized reflections (reviewed in 143). These species have lost the stochastic distribution of ommatidial types observed in many other species. Presumably, these specialized regions contain photoreceptors that exhibit novel properties, perhaps combining features of dorsal polarized light detectors of the *Drosophila* dorsal rim area (140, 141, 144) with properties of normal color-sensitive ventral photoreceptors. Little is known about what might have changed in the processing circuitry downstream of such changes to the retina, and this uncertainty provides opportunities for future research.

Other adaptations, such as pooling of inputs for additional sensitivity in low light conditions at the expense of resolution in nocturnal bees (46, 47) and in the especially low-light–sensitive nocturnal hawkmoth *Deilephila* (71), may also have implications for the evolution of neural circuitry and cell types downstream of the retina, but we lack detailed examples to date. Evidence suggests that changes in lamina arborization provides a means of pooling inputs in the hawkmoth (122, 123), but it is unknown how such changes in arborization are controlled. In a similar example, mouse rod photoreceptors that function in dim light pool their outputs onto bipolar cells to increase sensitivity (7).

Evolution of Lamina Neurons

The number of LMC types in insects is highly conserved at five, with one known exception. Honeybees have at least six distinct LMC morphologies (109, 110) (**Figure 3*a*,*b***). In a situation reminiscent of the mystery cell in the retina, additional cells exist in the *Drosophila* lamina during development in just the right position to produce an additional LMC similar to the one seen in honeybees (60, 61) (**Figure 1*b***). During development, between the precursor cells that become L4 and L5, there are one or two additional undifferentiated cells that later undergo programmed cell death in *Drosophila*. These cells might instead be retained during honeybee development to produce an additional LMC type (types shown in **Figure 3*b***). These cells could have arisen via duplication and divergence from an existing LMC type, or they could have initially arisen as some intermediate combination of preexisting types, defined by combining factors that normally distinguish two other LMC types. Additional studies will be required to assess what function extra LMCs provide, how this additional type is specified, and if the function of the other LMCs or

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synaptic partners has been modified in turn. It is intriguing to imagine how such an additional cell type might have initially plugged in to existing circuitry and how such a modification was evolutionarily retained.

More subtle differences in the morphology of LMCs have been recorded between different species of Diptera (17, 20), but it is not clear whether such finer-scale differences in arborization patterns influence function. For instance, L2 and L5 exhibit different branching patterns in species in the Glossinidae, Asilidae, and Tabanidae (the horse and deer flies) (17).

The direct coupling of retina development to lamina specification provides developmental flexibility, allowing individuals in a population to adjust to differences in extrinsic conditions that affect overall growth rate, such as nutrition: Whereas the number of ommatidia varies widely with the nutritional status of the fly, the number of lamina cartridges is precisely correlated with the number of ommatidia produced by the retina. This developmental flexibility may also be useful for accommodating evolutionary changes in the number or types of cells produced. For example, extra lamina differentiation-inductive signals from an increased number of photoreceptors in Hymenoptera (a second R7 cell) might make it easier to recruit an additional lamina type.

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The Evolutionary Implications of Temporal Patterning in the Medulla

There are few published examples of differences in specific medulla cell types in other insects, in part because of their deep conservation (17, 19, 20), but also because such differences are difficult to pick out among the >80 neural types, which often exhibit complex morphologies within a species. There may be yet undiscovered neural types even in the *Drosophila* medulla. One example of variation across species is found in the arborization of T5 neurons across the Diptera. In the Tipulidae (the crane flies), the arbors of T5 spread deeper into the medulla than they are wide, whereas in a species of Tabanidae, T5 is approximately as deep as it is wide. Then, in a species of Dolichopodidae, T5 arbors are wider than they are deep (17) (**Figure 3*d***). Such differences should influence the number of columns with which this cell type interacts and modify which medulla layers provide input. Without further characterization and understanding of this cell type and these morphological differences, it is unclear what impact such changes might have. Other examples of changes in arborization shapes and sizes exist in the literature for a range of visual system cell types (e.g., 17, 20), but it is not yet clear if these changes influence cell-type function.

The developmental mechanisms that underlie medulla patterning may themselves suggest hypotheses about how cell-type diversity evolved. The temporal series in the *Drosophila* ventral nerve cord contains four transitions characterized by expression of Hb → Kr → Pd → Cas → Grh, but not all neuroblasts transition through all factors: NB7–3 stops early and does not express Cas or Grh (63, 99; reviewed in 16). The temporal series in the medulla makes use of a different set of factors, characterized by the expression of Hth → Klu → Ey → Slp → D → Tll (**Figure 1*d***), but again not all neuroblasts transition through all factors: In the tips of the OPC, neuroblasts instead go through the sequence Dll → Ey → Slp → D, starting with a different factor and not progressing to Tll expression (11; reviewed in 81) (**Figure 3*e***). It is possible that by using only a subset of the temporal progression in certain neuroblasts, the types of neurons produced can be limited to a specialized subset. What this more limited neural diversity provides is unknown. An important open question is, which came first? Does the shorter series reflect an ancestral state to which new temporal windows have been added, or has there been a reduction in certain lineages? In either case, additional diversity could be generated by adding factors to the series at the ends or internally, and this may be how the series initially evolved. This raises fascinating developmental and evolutionary questions: By what mechanism can a new temporal

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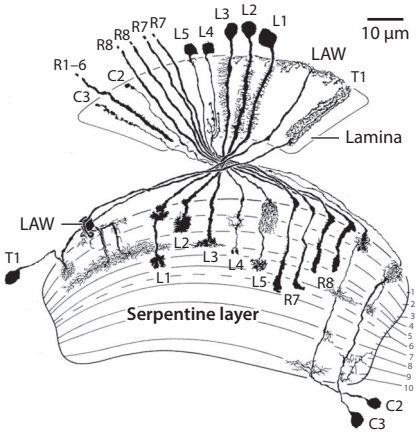
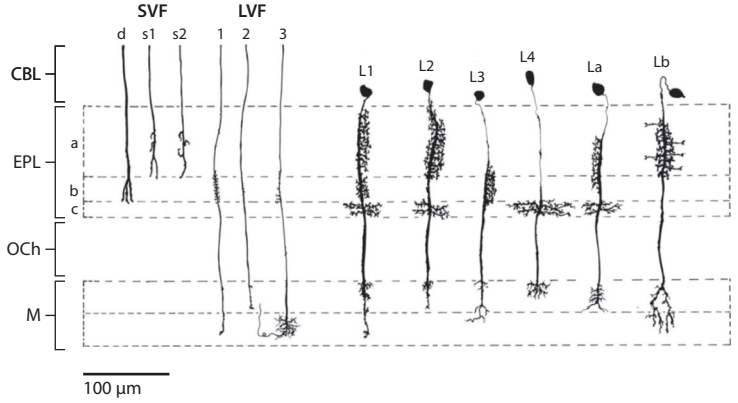
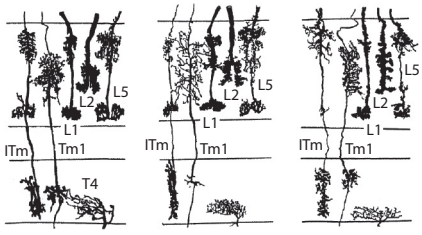
a *Drosophila* LMCs



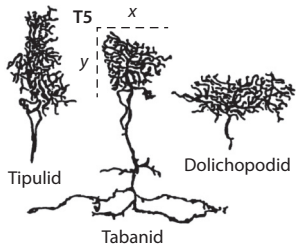
b Honeybee LMC types



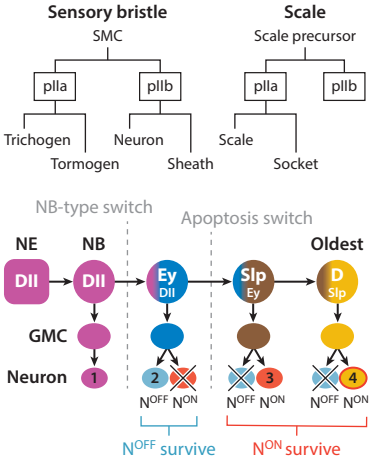
c Lamina variation



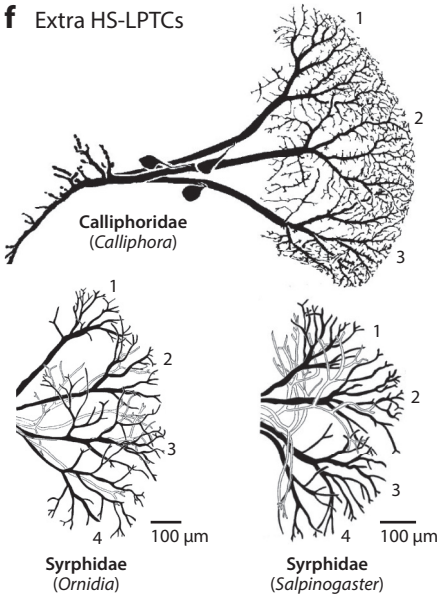
d Medulla variation



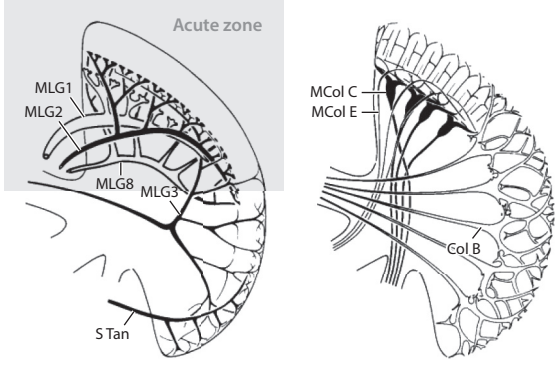
e Evolution of novelty



f Extra HS-LPTCs



g Male-specific neurons in *Calliphora*



factor be incorporated, and how do the neurons produced from a neuroblast during this new, different temporal window become useful for the animal?

In another example, limiting the types of cells produced via a preexisting developmental mechanism or lineage in a new context can lead to the evolution of novelty. For instance, the evolutionary modification of sensory organ precursor patterning can be compared to the modification of developmental mechanisms in the tips of the OPC. Sensory organ patterning that produces sensory bristles has been extensively studied (53). A limited portion of this lineage is now used to produce wing scales in butterflies (39) (**Figure 3*e***). In the development of bristles of the cuticle of the adult fly, a sensory mother cell divides once to produce two daughters, pIIa and pIIb, and then Notch signaling enforces different outcomes in each daughter cell (53). The pIIa cell divides to produce a trichogen and tormogen (a bristle and socket), whereas pIIb divides to produce a neuron and a glial sheath (53). In butterflies, the pIIa cell similarly divides to produce a socket and a scale instead of a bristle. Instead of producing a neuron and sheath, however, the pIIb lineage undergoes targeted cell death: Scales are not innervated. Despite not making use of the cells from this side of the lineage, they are first specified and then must be cleared out across the wing via apoptosis (39). In a similar way, the tips of the OPC not only use an abbreviated temporal series but also eliminate many of the neural types that would result from either Notch^{ON} or $\text{Notch}^{\text{OFF}}$ decisions of the neurons (11) (**Figure 3*e***). These undergo targeted cell death to produce a more limited set of neurons. The reuse of a subset of a core developmental specification pathway may be common in the evolution of neural diversity. It provides a means by which the number and types of neurons produced can be modified. New evidence has begun to suggest that temporal series also exist in vertebrates, which makes understanding how they evolve of broad interest (77, 85).

Evolution of the Lobula Plate

Some of the most dramatic examples of the evolution of additional neural types in the visual system are found in the lobula plate. The LPTCs are very large, highly branched neurons that contact many cells distributed across the lobula plate in a retinotopic fashion (55). Each LPTC is sensitive to specific characteristics of global motion and sends this information to the central brain (14, 84).

Figure 3

Diversification of insect visual systems. (*a*) Diagram showing morphology of *Drosophila* lamina cell types and the LMCs L1–L5 (33, 76, 91). (*b*) Honeybees have six (or more) distinct LMC morphologies (109, 110), suggesting they may have additional LMC types. (*c*) Lamina cell types are thought to be highly conserved across the Diptera but vary in morphology in a way that may influence connectivity and neural circuits. Here, L2 and L5 arborization patterns vary between Syrphidae and *Tabanus* species (17). (*d*) The medulla also has neurons that vary in arborization patterns across species; T5 is shown here in three families (17). These changes modify the number of columns contacted by T5 in each species. (*e*) Existing cell-fate specification mechanisms can be reused in new contexts in the evolution of novelty. Here, bristle specification pathways have been modified to produce butterfly wing scales, though half of the lineage undergoes targeted cell death in scales that are not innervated (39). This is strikingly similar to the use of a subset of the temporal series in the tips of the OPC, where, downstream of a Notch fate decision, half of each GMC lineage undergoes cell death to produce a more limited set of neural types (11). (*f*) *Ornidia and Salpinogaster* hoverflies (Syrphidae) produce four HS-LPTCs instead of the three found in *Calliphora* or *Drosophila* (20, 98). (*g*) Additional diversity can be sexually specific, as in the male-specific neurons in the *Calliphora* lobula plate that correspond to input from the dorsofrontal acute zone (124). Abbreviations: CBL, cell body layer; EPL, external plexiform layer; GMC, ganglion mother cell; HS-LPTCs, lobula plate tangential cells of the horizontal system; LAW, lamina area widefield; LMC, lamina monopolar cell; LVF, long visual fiber; M, medulla; MCol, male-specific columnar neurons; MLG, male-specific lobula giant tangential neurons; N, Notch; NB, neuroblast; NE, neuroepithelium; OCh, optic chiasma; OPC, outer proliferation center; SMC, sensory mother cell; S Tan, south tangential neuron; SVF, short visual fiber. Panel *a* modified with permission from References 33, 76, and 91; panels *c* and *d* from Reference 17; panel *e* from References 11 and 39; panel *f* from Reference 20; and panel *g* from Reference 124. Panel *b* adapted from References 109 and 110.

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For example, LPTCs of the vertical system (VS) are most sensitive to vertical motion and rotation around the equatorial plane of the animal (14, 78). Similarly, LPTCs of the horizontal system (HS) are tuned to horizontal motion (14). Large flies (*Calliphora* and *Musca*) and *Drosophila* have three HS cells that contact input cells corresponding to the ventral, medial, and dorsal regions of the retina (20) (**Figure 3*f***). *Eristalis* hoverflies have four HS-LPTCs instead of three (20, 98), which might play a role in the common hoverfly behavior of rotating around a vertical axis while hovering (**Figure 3*f***). In contrast, robber flies (Asilidae) exhibit ballistic flight behavior; they lack many or all VS-type LPTCs and instead possess additional HS cells in their place (20). In another case, a stalk-eyed fly has many fewer LPTC types, perhaps because of the unusual organization of its visual processing centers, which are found at the ends of long stalks adjacent to the eye (18). It has been suggested that the reduction in wide-field VS-type LPTCs may enhance the conduction velocities of these cells but result in a loss of spatial resolution in these extreme eyes (18). Despite a highly conserved pattern and distribution of input neural types in the lobula plate (19), evolution can act to modify how these signals are propagated and sent to the central brain by changing the complement and distribution of LPTCs (20).

Another example of a specialized LPTC comes from sexually dimorphic neurons in flies. Male *Calliphora erythrocephala* do not have a broad, regionalized Love Spot as male *Musca* do. One retina was carefully mapped by examining the yellow, pale, or red fluorescence of pigments under blue illumination (as described for *Musca* above) and using electron microscopy. This *Calliphora* male was shown to have only four widely separated Love Spot–type ommatidia (149). In these few sparse ommatidia, the rhabdom of R7 extends proximally to run alongside the R8 photoreceptor rhabdom, moving outward into a position more typical of an outer photoreceptor. Despite lacking a larger dorsal–frontal region composed of Love Spot–type ommatidia, they have enlarged ommatidia in a similar area in an acute zone. In corresponding regions of the lobula plate, male *Calliphora* and *Sarcophaga* have additional types of LPTCs (e.g., male-specific lobula giant neurons) and columnar neurons (e.g., male-specific columnar neurons) in the lobula plate that are thought to function specifically in target detection (43, 124) (**Figure 3*g***). Such changes in the lobula plate for target detection are not entirely expected, given that the lobula plate is thought to be primarily used for detecting global, broad-field motion of the fly relative to its surroundings (14). Male *Musca* might also have similar specialized neurons in the Love Spot region (56). More recently, *Eristalis* hover flies were also found to have a sexually dimorphic horizontal system LPTC in a region corresponding to the dorsal part of the male eye, also presumably to facilitate female-chasing behavior (98, 135). How information is transmitted from the lobula plate to the central brain seems to vary across species, and this step in visual information processing is a hotspot for evolutionary changes to the distribution of neural types in the visual system.

EVOLUTION OF NEURAL CIRCUITS

The evolution of new neural types is perhaps more complicated than the evolution of other cell types because neurons are highly interconnected with many other neurons. Changes in one cell type will affect the physiology of others and the circuit in which they are embedded, impacting how information is processed. Existing models of cell-fate evolution via divergence or subfunctionalization may provide a useful framework (4, 5), although the high degree of connectivity in the brain leads to additional complexity. New neural types must plug in to existing circuitry: either the interconnected neurons must be plastic enough to compensate and make use of the added input at the circuit level, or there must be corresponding changes to the number and types of neurons in the circuit, perhaps downstream of the added neuron. We focus on two specific cases discussed previously: the Love Spot and the evolution of a second R7 photoreceptor.

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Lepidoptera (and possibly Hymenoptera) have twice the number of R7 photoreceptors per ommatidium compared to *Drosophila*, and this might impact the number of R7-interacting cells in each medulla column. The two R7s per ommatidium may simply pool their input into the same number of downstream cells as *Drosophila* in each medulla column, but this seems unlikely given the observed differences in Rhodopsin expression downstream of stochastically expressed Spineless: Some express a UV-sensitive Rhodopsin, whereas others express blue-sensitive Rhodopsin (105), and sometimes both are present together in the two R7s of a single ommatidium that sends axons to the same medulla column. In *Drosophila*, R7s connect to three cell types, Dm8, Tm5a/b/c, and Tm20 (83, 92). This raises the question, do butterfly medullas have twice as many cells of the types that contact the two R7s? The answer may depend on whether the system was able to compensate for such a change at the circuit level (neural plasticity) or developmentally in terms of preexisting developmental ability to produce or retain additional matching partners (developmental plasticity).

In another example, male-specific LPTCs evolved to convey additional information from the region receiving input from the Love Spot to the central brain (58). This suggests that different cell types evolved in a coordinated way to achieve a specific function, in this case, in order to detect and chase females. Such coordinated addition of cell types for shared function could have led to the evolution of new circuits. In the Love Spot, the R7s were transformed into motion detection photoreceptors and added sensitivity to an existing circuit. This contributed input from seven photoreceptors instead of six, with the new input added specifically into the OFF dark edge detection motion pathway. Specialized dorso-anterior LPTCs presumably provide additional channels for sending information collected from this part of the visual field on to the central brain. An additional change has been observed here at the circuit level: The output of R8 photoreceptors can no longer be compared to that of R7s in the medulla, and R8s appear to be extraneous. However, these Love Spot R8s now synapse heavily onto R7s as they pass through the lamina, suggesting that they share their input with R7s (49) and thus also contribute to target detection pathways. By adding synapses between R8 and R7, the functionality of these orphaned R8s may be restored by contributing to the OFF motion vision circuit.

In other cases, circuits may remain constant and adapt to evolutionary pressure differently. In the case of the *Drosophila* olfactory system, the circuits are well defined: Sensory neurons that express the same olfactory receptors converge on a distinct ganglion/glomerulus, where they connect to projection neurons, which in turn transfer olfactory information to the mushroom body, whose main role in flies is olfactory memory. Different drosophilids encounter vastly different olfactory environments to which they need to adapt. Although one can observe differences in the number of olfactory glomeruli and the range of olfactory receptors used (40, 42, 97), the circuits seem to remain unchanged (106). Similarly, in the visual system, the expression of different Rhodopsins in photoreceptors has changed across species (143), increasing or decreasing sensitivity for specific wavelengths without actually changing the circuit downstream of the photoreceptors. It will be interesting to determine if such changes in Rhodopsin expression have ever given rise to later changes at the circuit level, in terms of which inputs are compared.

ORIGIN OF NEUROPILS

Among the arthropods, insects and Malacostraca have the most complex visual information processing systems with four distinct optic lobe neuropils: the lamina, medulla, lobula, and lobula plate (**Figure 4*a***). Most other arthropods have just one or two neuropils. This begs the question, which neuropils are ancestral, and how did newer neuropils arise?

Directly under the retina of all arthropods is the lamina, where short visual fiber photoreceptors first arborize. The simplest arthropod visual system is found in the velvet worms (Onychophora),

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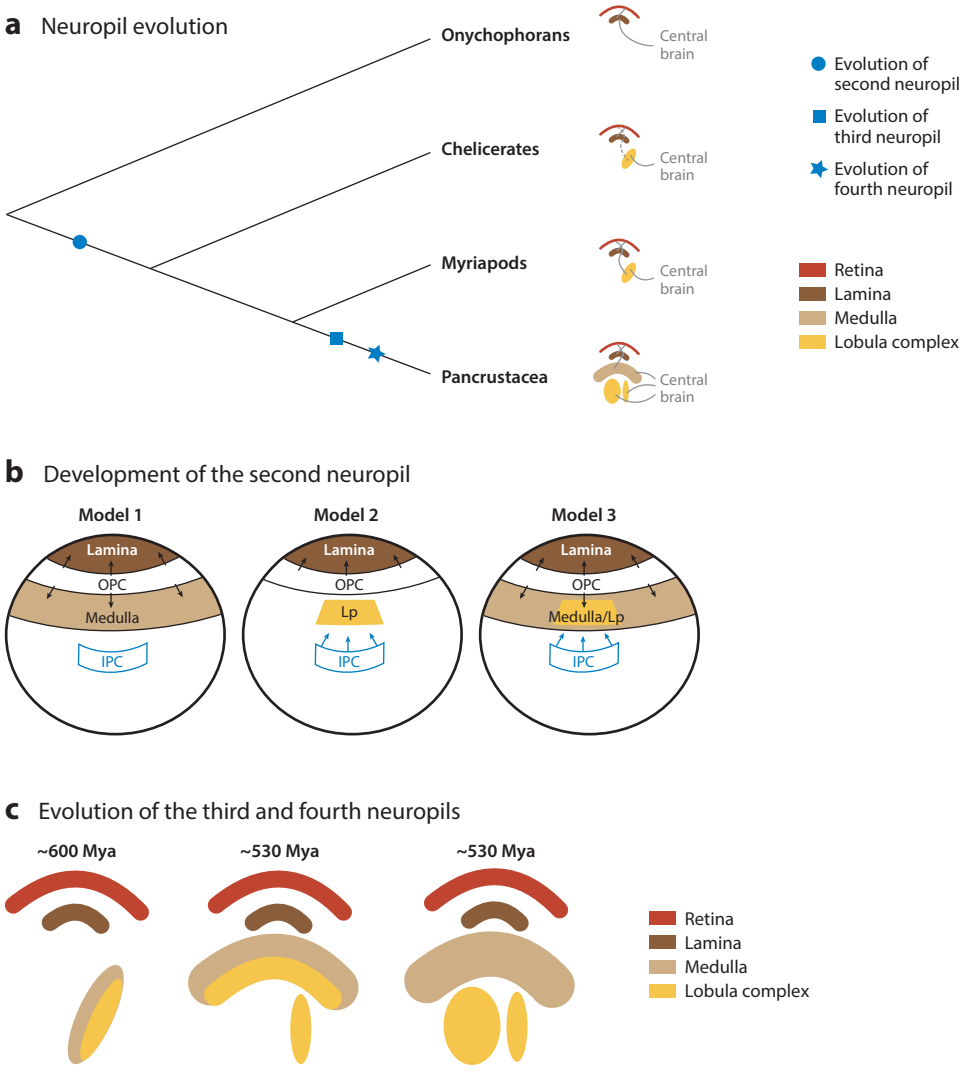

Figure 4

Neuropil evolution in the arthropods. (*a*) Phylogenetic tree of the arthropods indicating the major events in the evolution of visual system neuropils, i.e., the emergence of the second, third, and fourth neuropils. Diagrams on the right show a representative brain for each group. (*b*) There are three models regarding the homology of the second neuropil to the medulla or the lobula plate (LP) of extant insects. In model 1, the second neuropil is homologous to the medulla, which is generated by the outer proliferation center (OPC) (125). In this case, the inner proliferation center (IPC) also likely produces some medulla cell types. Alternatively, in model 2, the second neuropil is homologous to the LP (54), which, in extant insects, is generated by the IPC (3). Finally, in model 3, a hybrid of the extant medulla and lobula complex develops from both the OPC and IPC and may have been the second neuropil of the common ancestor of the Euarthropoda (118). (*c*) Given our current understanding of medulla and lobula complex development in *Drosophila*, the third model is the most parsimonious. In this case, chelicerates, myriapods, and branchiopods have a second neuropil that exhibits features of both the medulla and lobula complex. The first division of this neuropil generated a medulla/lobula hybrid ancestor, which was then duplicated or split into what we know today in *Drosophila* as the medulla and lobula.

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which possess only a lamina. From there, lamina cells project either directly to the mushroom body (which in velvet worms is mainly involved in visual memory) or to the central brain, where visual information must be extracted with little prior processing (88). Onychophora have only broad-wavelength Rhodopsins and thus must perceive only light and motion but not shapes or colors (57). They have neither color-sensitive Rhodopsins nor a medulla, which more complex invertebrates use to process color information. It would be interesting to know which evolved first: specifically expressed, wavelength-specific Rhodopsins or a more specialized way to process these signals. In either case, more complex visual processing required the evolution of additional neuropils.

Evolution of the Medulla and Lobula Complex

All Euarthropoda have at least two neuropils. The first is the lamina, in which cell-type composition is largely evolutionarily conserved, as discussed previously. The second neuropil evolved in a common ancestor of the Euarthropoda, probably preceded by the duplication or splitting of the single proliferation center into two, the OPC and the IPC. Whether the resulting additional neuropil is homologous to the medulla or to the lobula plate of extant insects is still open for debate (54, 118, 120, 125). Three models have been proposed to account for the identity of this second neuropil (**Figure 4*b***). They are:

- Model 1: The second neuropil was homologous to the medulla of extant species. In this case, the OPC neuroepithelium originally gave rise only to the lamina but then gained the ability to also generate the medulla on the side opposite from the lamina.
- Model 2: The second neuropil is homologous to the lobula plate of the extant insects. In this case, the lamina is still generated by the OPC, whereas the lobula plate is generated by a homologous duplication of the OPC structure, the IPC (54).
- Model 3: The second neuropil was a precursor to both structures and performed functions that are now distributed among all three neuropils (medulla, lobula, and lobula plate). It later divided, initially to form a medulla/lobula precursor and lobula plate, and then into a medulla, lobula, and lobula plate (118) (**Figure 4*c***).

The third and fourth neuropils, whether they are the lobula complex or the medulla and lobula, evolved within the crustacean-hexapod lineage. Branchiopods (like myriapods) have only two neuropils, whereas malacostracans and hexapods have four (**Figure 4*a***) (125). The phylogenetic relationships among branchiopods, malacostracans, and hexapods are not fully resolved; however, the brain structure strongly supports an early split of the branchiopods from the malacostracan/hexapod lineage (126). The evolution of the lobula could be explained by two hypotheses—one stating that it separated from the medulla (**Figure 4*c***) and the other that it originated in the central brain in the form of a protolobula coming from the lateral protocerebrum (118, 125).

Using Development to Understand Evolution

Our understanding of brain development in *Drosophila* has made rapid progress in recent years, providing fresh insight into evolutionary questions. Several developmental processes support model 3 described in the previous section (**Figure 4*c***). They include the following:

- The tips of the OPC (tOPC) are different from the rest of the OPC. Their neuroblasts progress through a slightly different temporal series (11). Perhaps the most striking difference is the cell types they generate. Whereas the OPC exclusively generates the lamina and the medulla, the tOPC gives rise to neurons that populate the medulla, lobula, and lobula plate

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(11). Given that the OPC was originally responsible for generating neurons of the only neuropil (the lamina), it is intriguing to consider that, in the last common ancestor of all Euarthropods, the tOPC generated neurons for a single ancestral neuropil that was then subdivided or duplicated to produce the three neuropils in which the tOPC neurons still arborize.

- T4 and T5 (the cells primarily responsible for transferring motion detection information to the lobula plate) arise from the same pool of progenitors that derive from the IPC, and they are highly related apart from the fact that T4 arborizes in medulla layer 10 and T5 in lobula layer 1 (3). It has been suggested that T4 and T5 share a common ancestor involved in motion detection that was later duplicated into T4 and T5, which, in turn, diverged and became responsible for detecting ON and OFF edges, respectively (118). One can imagine the T4/T5 ancestral cell type arborizing in the last layer of the medulla/lobula precursor neuropil before this split into medulla and lobula, as we know them today.
- Finally, two new types of lobula plate-intrinsic interneurons were discovered recently, LPi3-4 and LPi4-3 (87). Although LPi3-4 arborize only in the lobula plate, they are generated by the OPC and their cell bodies lie in the cortex of the medulla. This suggests that medulla and lobula plate once had a common ancestor, which was generated in part by the OPC. Given that both LPi neurons participate in the motion detection circuit and connect to the LPTCs of lobula plate layers three and four (87), this ancestral neuropil must have possessed features from both medulla (development from the OPC) and lobula plate (motion detection).

These arguments provide strong support for the third model. Studying such developmental mechanisms can provide insight into evolutionary questions. Conversely, in the light of evolution, previously nonintuitive developmental mechanisms (e.g., the differences in the temporal series of the tOPC and main OPC, as well as the nature of the neurons produced) can be put in better perspective.

Cell-Type and Neuropil Evolution

This initial look at how neural types are generated and where they are produced has provided insight into how the additional neuropils evolved, but questions remain. How is cell-type evolution coupled to neuropil evolution? Which came first, the split between T4 and T5 or the addition of a new neuropil followed by divergence in cell fates? If a new neural cell type evolved first, it might need a place to connect as well as some additional utility, such as providing novel function or adding robustness to an existing pathway. Evolution of the Love Spot R7 in flies and the second R7-like photoreceptor in butterflies provides specific examples. Perhaps by accumulating additional neural types it then becomes easier to evolve a new neuropil to accommodate additional connections. Conversely, the generation of a new neuropil might allow duplicated neurons to subfunctionalize or diversify further. The wholesale duplication of a neuropil might in some ways be analogous to duplication of the entire *hox* cluster: Instead of copies of individual *hox* genes, some neural types might be lost upon duplication of a neuropil, whereas others might diverge and allow for the evolution of additional complexity.

In the case of T4 and T5, it is possible that the neurons that provide the basic components of motion vision are ancient and are among the first types evolved. In this model, a similar, homologous cell type would have been present in the less complex common ancestor. It would then be useful to examine extant relatives of that ancestor that have a single optic neuropil (such as velvet worms) to ask whether they have a T4- and/or T5-like cell type. Taking advantage of the tools of *Drosophila* and new sequencing technologies, it should be possible to identify core sets of transcription factors that define cell types (as suggested in 5) to test for deep homology. Such an

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approach will provide the opportunity to select animals from different phylogenetic groups and study specific cell types to gain insight into how these cell types are specified and what functions they provide. This would allow us to establish cell-fate homologies and better understand the evolution both of neural cell types and of entire neuropils in detail.

FUTURE CHALLENGES

Specification of the correct neurons at the proper time and place during development produces a nervous system capable, at its most basic level, of perceiving a range of stimuli and producing a range of behavioral responses. Understanding how cell types and circuits integrate and process sensory input and then use this information to produce specific behavioral responses has become a major focus in biology. When considering the complexity of the brain with all its individual neurons, it seems a nearly impossible problem to understand what types of changes to an existing nervous system might become useful for an animal. A powerful approach has been to turn this question around and to first identify specific cases where a behavior or preference has changed between species, and then to use comparative genetic or developmental approaches to understand what it is that controls these differences (e.g., 59, 139). Such examples have provided insight into how behaviors can be modified by changes at one or a few loci. Developmental approaches are then necessary to understand what role these cells play and how these changes influence neural circuit-level processing, as well as to test the functional role of specific candidate genes directly. The development of new tools such as cheaper sequencing, cell type–specific sequencing, and CRISPR/Cas9 allow for an increasing level of sophistication of experiments directly in nonmodel species. Expanding comparative approaches that combine tools such as quantitative genetics with experimental developmental biology will be critical for fully understanding the genetic and mechanistic basis of neural function and evolution.

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