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Wiring visual systems: common and divergent mechanisms and principles

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The study of visual systems has a rich history, leading to the discovery and understanding of basic principles underlying the elaboration of neuronal connectivity. Recent work in model organisms such as fly, fish and mouse has yielded a wealth of new insights into visual system wiring. Here, we consider how axonal and dendritic patterning in columns and laminae influence synaptic partner selection in these model organisms. We highlight similarities and differences among disparate visual systems with the goal of identifying common and divergent principles for visual system wiring.

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Introduction: pre- and post-specification of visual system synapses during development

Invertebrate and vertebrate visual systems map color, motion, and feature information onto retinotopic visual maps in the brain. However, the actual anatomical structures are quite different. Fly photoreceptors (R cells) are the primary retinal output neurons that carry visual information to the first and second visual system relay stations (Figure 1A). In contrast, visual information from photoreceptors in the vertebrate eye is extensively processed within the retina. Like R cells in flies, vertebrate retinal ganglion cells (RGCs) convey information to the first visual system relay stations in the brain, including the optic tectum/superior colliculus (OT/SC), lateral geniculate nucleus (LGN), and numerous other retinorecipient nuclei. Hence, with respect to retina output, fly R cells and vertebrate RGCs are comparable (Figure 1A). In contrast, at the level of connectivity and visual information processing, the two synaptic plexiform layers upstream of RGCs in the vertebrate retina are comparable to brain neuropils downstream of R cells in the fly optic lobe (Figure 1B): the vertebrate retina outer plexiform layer (OPL) to the fly lamina, and the inner plexiform layer (IPL) to the fly distal medulla [1]. These comparisons make sense in terms of circuit connectivity and function, but the actual structures and cell types are not analogous. For example, a subset of RGCs that are intrinsically photosensitive reveal that RGCs may share evolutionary origins with invertebrate photoreceptor neurons [2,3]; vertebrates may have evolved modern retinal connectivity subsequent to development of the first photosensitive cells, while connectivity in the fly lamina and medulla may have evolved independently and downstream of retinal output (Figure 1A,B).

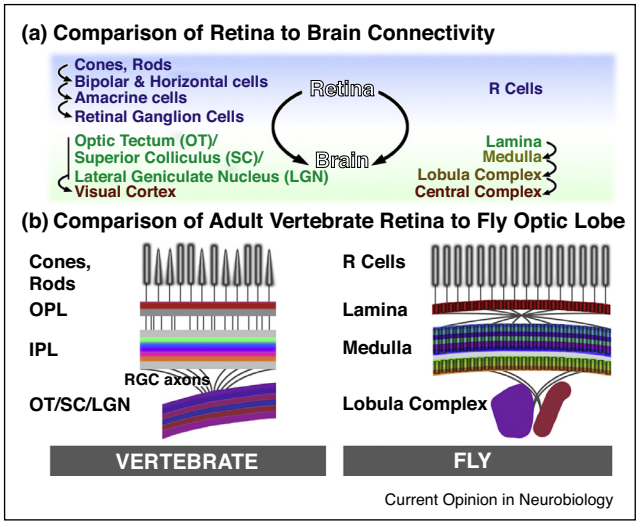
Similar design principles among disparate visual circuit ensembles may be best appreciated in the context of shared developmental processes that orchestrate iterative patterns of synaptic connectivity [4]. Synaptic specification is determined by two core processes: (1) precision of wiring before initial synapse formation (*pre-specification*); and (2) pruning and fine-tuning of connections (*post-specification*). In vertebrates, activity-dependent fine-tuning of synaptic specificity plays an important role in visual system connectivity, showcasing the importance of post-specification (Figure 2) [5,6,7•]. In contrast, visual system wiring in *Drosophila* appears to be predominantly determined by a genetic program, highlighting pre-specification (Figure 2) [4,8,9]. However, in both systems pre- and post-specification likely work hand in hand: initial axonal and dendritic targeting to distinct columnar or laminar structures provides important milestones along the road to mature synaptic specificity [1,4,10••,11].

In fly and vertebrate visual systems, processing of parallel information streams is morphologically preserved in repetitive columns or mosaics of similar cell types. Orthogonal to this lateral organization is the prevalent subdivision of visual system components into layers, or laminae; these elements provide anatomically restricted regions where presumptive synaptic partners are in close proximity and facilitate synaptic partner identification, revealing common and divergent developmental principles across visual systems.

Columns and mosaics in synaptic specification

During development, vertebrate cones and rods extend short axon terminals that contact horizontal cell dendrites

Figure 1



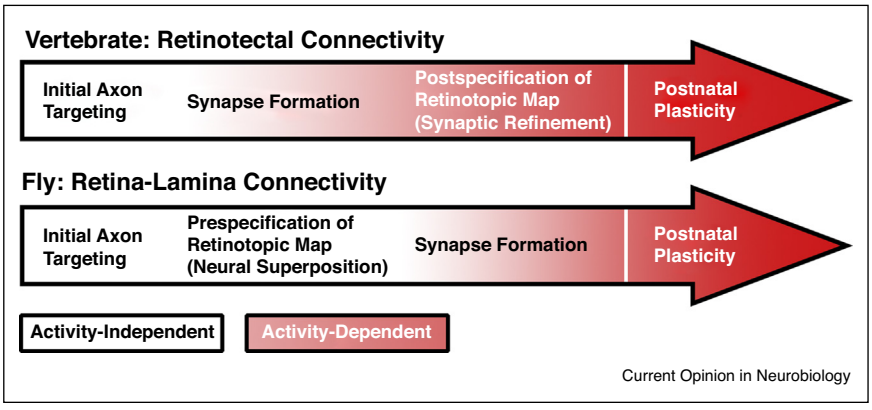
Adult vertebrate and fly visual system wiring. **(A)** Comparison of retina-to-brain connectivity based on retina output neurons and possible evolutionary relationships between vertebrate RGCs and fly R cells. **(B)** Comparison of vertebrate retina to the fly optic lobe-based on similarities of functional connectivity.

and axons, respectively, and also cone and rod bipolar cell dendrites. Since photoreceptor projections to these interneurons are short and anatomically parallel, retinotopy is maintained in both the OPL and IPL (Figure 3A). In contrast, during larval development fly photoreceptors extend long axons that project from the developing eye disc into the brain (Figure 3B). Vertebrate retina output neurons, RGCs, also maintain retinotopy in their central projections to certain retinorecipient regions. Topographic mapping of RGC axons onto the tectum/superior colliculus is facilitated by orthogonal EphA/ephrin-A and EphB/ephrin-B gradients [5]. These gradients establish topographic mapping through relative, not absolute, levels of ephrin signaling to RGC axons [5,12]. *Drosophila* has a single Eph gene that is expressed in a gradient in the early developing medulla, so fly R cells may also respond to relative, and not absolute, levels of Eph receptor activity [13]. Therefore, Eph/ephrin signaling may contribute to synaptic pre-specification without providing an absolute synaptic address system.

In flies, adjacent columns that process information from neighboring visual fields are called 'cartridges' in the lamina and 'columns' in the medulla. Lamina cartridges exhibit an intricate wiring pattern that reflects the optical organization of the retina according to the principle of neural superposition [1,8,9]. Neural superposition is an interesting case of pre-specification. Owing to the optics of the overlying retina ommatidia, each lamina cartridge receives input from six R cells that each project from a different ommatidium. Though this creates an intricate wiring problem, a few simple pattern formation rules can generate correct axon sorting [14•,15]. This sorting step is genetically separable from synapse formation, and in large part pre-specifies synaptic partners since the correct number of synapses form between incorrect partners when sorting is aberrant [8]. These simple rules must be executed by molecular mechanisms that ensure patterning and such mechanisms have been identified, providing support for the idea that 2-dimensional differential adhesion is achieved through the action of cell adhesion molecules such as N-cadherin and the proto-cadherin Flamingo [9,16•]. The sorting process synchronously organizes each column without the need for a large number of different cues to selectively label neighboring columns, demonstrating the utilization of cell adhesion molecules to establish overall patterning of connections as opposed to synapse-specific targeting cues.

In the vertebrate retina no clear columnar organization develops that maps, point-to-point, neighboring regions of the visual field to synaptic ensembles. However, in the

Figure 2



Pre-specification and post-specification of synapses in vertebrate retinotectal connectivity versus fly retina–lamina connectivity.