Architecture, Function, and Assembly of the Mouse Visual System

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Abstract

Vision is the sense humans rely on most to navigate the world, make decisions, and perform complex tasks. Understanding how humans see thus represents one of the most fundamental and important goals of neuroscience. The use of the mouse as a model for parsing how vision works at a fundamental level started approximately a decade ago, ushered in by the mouse's convenient size, relatively low cost, and, above all, amenability to genetic perturbations. In the course of that effort, a large cadre of new and powerful tools for in vivo labeling, monitoring, and manipulation of neurons were applied to this species. As a consequence, a significant body of work now exists on the architecture, function, and development of mouse central visual pathways. Excitingly, much of that work includes causal testing of the role of specific cell types and circuits in visual perception and behavior—something rare to find in studies of the visual system of other species. Indeed, one could argue that more information is now available about the mouse visual system than any other sensory system, in any species, including humans. As such, the mouse visual system has become a platform for multilevel analysis of the mammalian central nervous system generally. Here we review the mouse visual system structure, function, and development literature and comment on the similarities and differences between the visual system of this and other model species. We also make it a point to highlight the aspects of mouse visual circuitry that remain opaque and that are in need of additional experimentation to enrich our understanding of how vision works on a broad scale.

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INTRODUCTION

The mouse is currently the preeminent model for studying visual circuit structure, function, development, and disease. This was not the situation a decade ago. Several factors prompted the surge in use of mice for studying the visual system. First, genetic tools in the mouse readily

permit analyses of gene function and neural circuit architecture at the level of defined cell types and connections. Second, light-based parameters can be tightly controlled and delivered both in vitro (to the retina) and in vivo to the whole animal, enabling one to address how specific aspects of sensory information are processed by the mammalian central nervous system. Third, in the mouse, large-ensemble monitoring and manipulation of neuronal activity patterns are possible in vivo (Ackman et al. 2012, Sohya et al. 2007, Stirman et al. 2016, Zhang et al. 2011) and can be combined with behavioral analyses (Glickfeld et al. 2013b, 2014; Ko et al. 2014; Mrsic-Flogel et al. 2005; Roth et al. 2016). What have we learned as the result of the tremendous amount of experimental attention and effort that have been placed on the mouse visual system, and where does that information place us with respect to understanding how human vision works? Previous reviews dealt with the relative advantages and disadvantages of using the mouse as a model for vision (Baker 2013, Huberman & Niell 2011). Here our objective is to provide an in-depth reference for what is now known about the organization, function, and assembly of mouse visual circuits in order to better define the major conceptual and experimental paths needed going forward and, more generally, to deepen understanding of how vision works.

OVERALL ORGANIZATION OF THE MOUSE VISUAL SYSTEM

The organizational logic of the mouse visual system is based on the presence of local circuits housed within given neural structures and cortical areas, and long-range connections that link those local circuits together. Most visual connections transmit information about visual space (e.g., a specific location within the visual field) and a feature within that space (e.g., motion, direction, or a particular color). The two most heavily studied maps of visual space are retinotopy and eye specificity (**Figure 1**). Within these two spatial maps, other aspects of visual stimuli such as orientation, direction, and color are represented and processed. This selective processing of individual visual features is carried out by segregating cells and their neurites into distinct layers, maps, and subcellular wiring patterns (**Figure 2**). Below we review the layout and organizational logic of visual features and describe how the brain transforms their representative neural signals as they flow progressively up the neuraxis.

Mouse Retinal Circuits and Cell Types: A Brief Overview

Analysis of visual scenery begins with photoreception. The mouse has both rods and cones, but the rods, which operate best at low-light conditions, vastly outnumber the cones. There are two major cone types in the mouse, each with different spectral sensitivities—green and blue—as well as a third type composed of mixed green/blue photopigment expression. Interestingly, the spatial layout of the cone photoreceptors is not uniform across the retina (Szél & Röhlich 1992). One consequence of this arrangement is that the processing of specific color qualities, as well as contrast, varies across the visual field in an ethologically optimized way, allowing selective processing of certain features in the sky-versus-ground portions of the scene (Applebury et al. 2000, Baden et al. 2013, Haverkamp et al. 2005, Szél & Röhlich 1992; reviewed in Wernet et al. 2014).

After photoreceptors convert light information into electrical signals, the retinal interneurons—the horizontal, bipolar, and amacrine cells—filter and shape those signals and transmit them to the output neurons of the eye, the retinal ganglion cells (RGCs). The spiking activities of the RGCs are then sent to the brain, where they drive visual percepts and light-mediated behaviors. Currently, there are believed to be ~33 different RGC types, each of which responds best to a particular aspect of the visual scene (Baden et al. 2016). For a more in-depth description of the various RGC types and how they are thought to relate to central visual processing, we

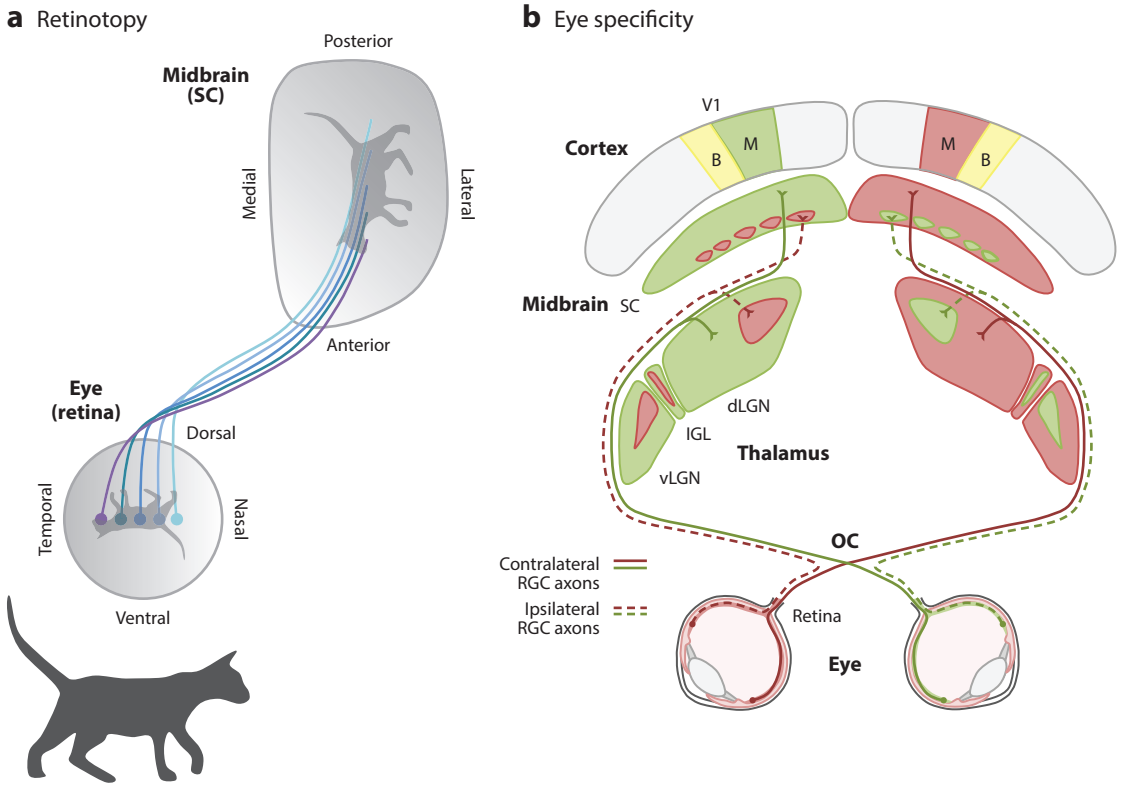


Figure 1

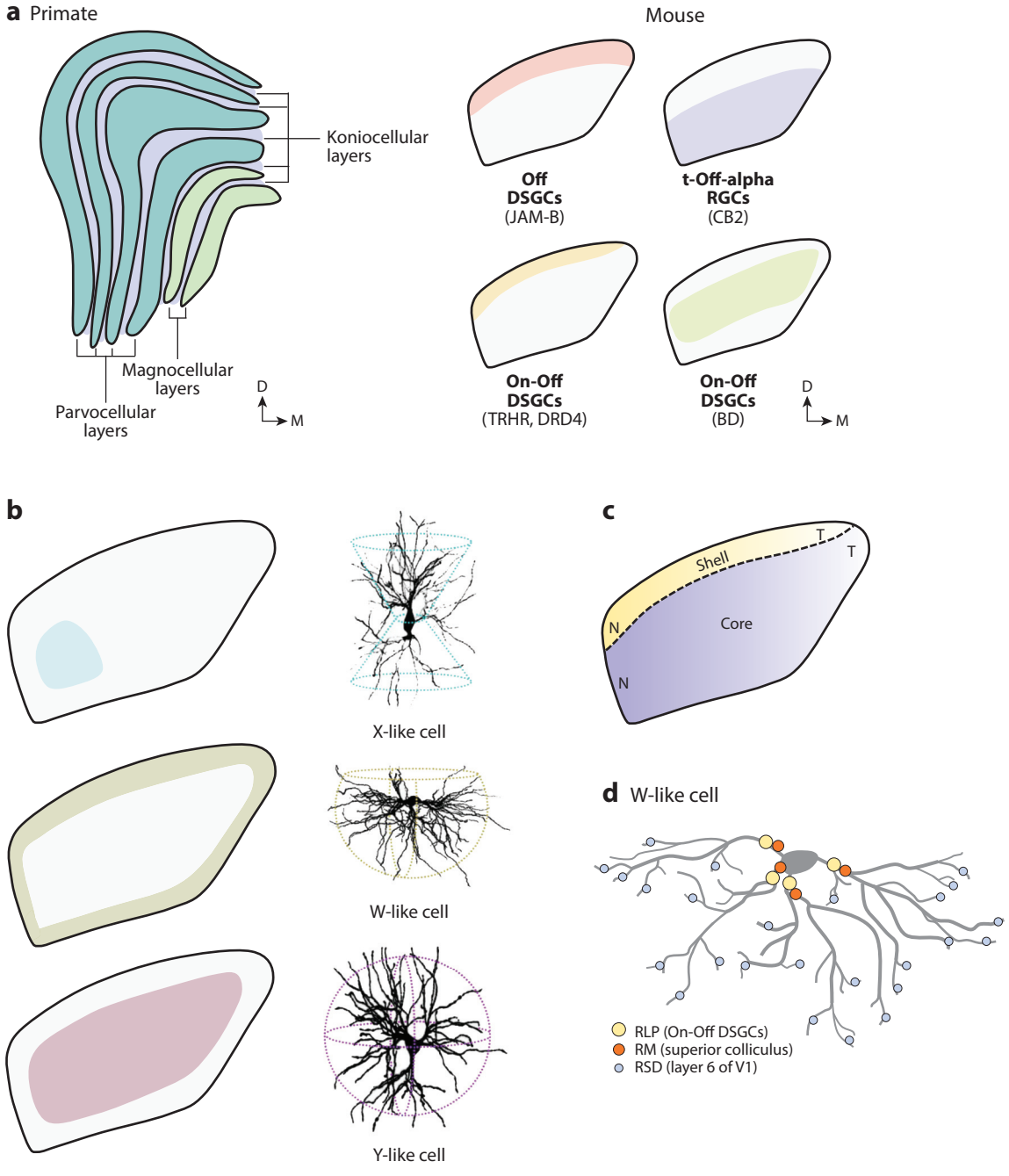
Mapping visual space from the retina to the brain in the mouse. (*a*) Neighboring points in a visual scene are mapped onto neighboring neurons in the retina. The spatial order of these retinotopic maps is preserved in targets of RGCs such as the SC. (*b*) Axonal projections from the two eyes are segregated into distinct domains within some retinorecipient targets that receive binocular input. This eye specificity is visualized by injecting different colored anterograde tracers into each eye. dLGN neurons send their axons to V1, which in mouse is composed of two zones. The monocular zone (M) receives information via dLGN exclusively from the contralateral eye, whereas the binocular zone (B) gets input from both eyes. Other abbreviations: dLGN, dorsal lateral geniculate nucleus; IGL, intergeniculate nucleus; OC, optic chiasm; RGC, retinal ganglion cell; SC, superior colliculus; V1, primary visual cortex; vLGN, ventral lateral geniculate nucleus.

Figure 2

Laminar specificity of the dLGN. (*a*) Retinorecipient targets, such as the dLGN, are subdivided into layers, which receive distinct qualities of afferent retinal input. The dLGN of the mouse, unlike that in the primate, does not have cytoarchitectural lamination. Labeling of different RGC subtypes using transgenic mice reveals that mouse dLGN does consist of functionally distinct layers. Panel adapted from Hong & Chen (2011) and Nassi & Callaway (2009). (*b*) Target neurons (relay cells) are located in discrete regions of mouse dLGN. Panel adapted from Krahe et al. (2011). (*c*) These functionally discrete layers each contain a complete retinotopic map. (*d*) Subcellular wiring of afferent input onto a W-like relay cell in the mouse dLGN. Panel adapted from Bickford et al. (2015). Abbreviations: CB2, calbindin 2; D, dorsal; dLGN, dorsal lateral geniculate nucleus; DRD4, dopamine receptor 4; DSGC, direction-selective ganglion cell; JAM-B, junctional adhesion molecule B; M, medial; N, nasal; RGC, retinal ganglion cell; RLP, round vesicles, large profiles, pale mitochondria; RM, round vesicles, medium profiles; RSD, round vesicles, small profiles, dark mitochondria; T, temporal; TRHR, thyrotropin-releasing hormone receptor; V1, primary visual cortex.

refer you to several recent reviews on this topic (Berson 2008; Demb & Singer 2015; Dhande & Huberman 2014a; Dhande et al. 2015b; Masland 2001, 2012; Métin et al. 1983; Roska & Meister 2014).

It is important to note that the spatial variation in photoreceptor types described above impacts the spectral tuning as well as other response properties of RGCs (Joesch & Meister 2016, Wang



et al. 2011). It therefore follows that such variations can influence various aspects of central visual processing. Additionally, several labs (Bleckert et al. 2014, Hughes et al. 2013, Zhang et al. 2012; R.N. El-Danaf & A.D. Huberman, submitted manuscript) have recently discovered evidence for large-scale variation in the density of different RGC types and their dendritic field sizes across the retina. This equates to large variations in their receptive field sizes according to their retinotopic location—the downstream consequence of which is that, within central visual pathways, there is enriched (or reduced) analysis of certain visual features as viewed in particular locations of the outside world. Moreover, there is also already clear evidence for dramatically uneven spatial representations of specific receptive field properties, such as motion, in certain higher cortical areas (Denman et al. 2017, Garrett et al. 2014, Rhim et al. 2017, Tan et al. 2015). These two sets of findings are intriguing and suggest that the mouse visual system includes many still-unrecognized subtleties, but little attention has yet been devoted to understanding the possible relationship between retinal cell type distribution and the organization and dynamics of central visual processing. In our opinion, one of the more important goals of the visual neuroscience field is to resolve this gap—especially given how strongly variation in the distribution of retinal cell type has informed our understanding of visual processing in primates and other species (Nassi & Callaway 2009, Tootell et al. 1982). In theory, mouse genetic tools allow for retinal and central neural circuits to be causally and unambiguously related to one another. In the meantime, the fact that certain photoreceptor types and a growing number of RGC subtypes display significant variation in their number, size, and connectivity across the retinal sheet underscores the idea that the mouse visual system is far more similar to that of primates and carnivores than previously thought—and it also reinforces the need for deeper study into how visual signals are transformed as they flow through the brain.

Image-Forming Versus Non-Image-Forming Visual Pathways

The broadest functional distinction that one can make regarding the organization of visual circuits is their separation into image-forming versus non-image-forming pathways. Image-forming circuits give rise directly to sight (i.e., locating and perceiving shapes, their locations, and their specific features such as their direction of movement). Non-image-forming circuits, by contrast, operate below the level of conscious perception to either support sight indirectly (e.g., pupil reflexes and involuntary eye movements that ensure image stabilization) or support light-based modulation of core physiological functions that take place over relatively long timescales and have no relationship to sight, such as entrainment of the circadian clock, regulation of hormone rhythms, sleep cycles, and pain sensitivity (Dhande et al. 2013, Hattar et al. 2003; Noseda & Burstein 2011, Yonehara et al. 2009).

The primary basis for the segregation between image-forming versus non-image-forming visual pathways is the partitioning of axonal projections arising from different RGC subtypes to different subcortical targets. As a whole population (all 33 subtypes), RGCs project to >40 subcortical retinorecipient brain targets (Morin & Studholme 2014), each of which mediates a distinct set of functions. The recent discovery and characterization of genetic tools for labeling specific RGC types in the mouse has opened the door for rich understanding of these retinal output pathways (reviewed in Dhande et al. 2015b, Roska & Meister 2014). Some of those structures, such as the dorsal lateral geniculate nucleus (dLGN), relay retinal information directly to visual cortex—the site of conscious perception—whereas others, such as the midbrain superior colliculus (SC), receive direct input from the retina but connect to cortex only through intermediate stations such as the lateral posterior nucleus (LP) or via feedforward connections to the dLGN (**Figure 3**). Importantly, many (but not all) non-image-forming retinorecipient structures receive

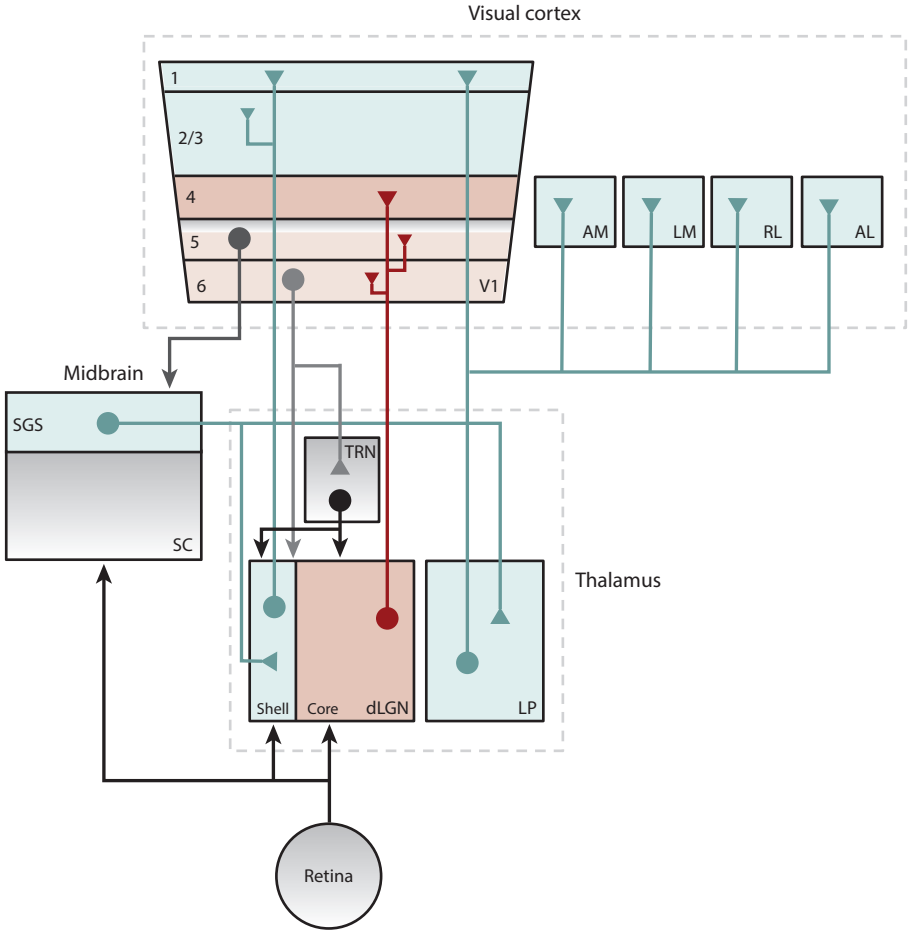


Figure 3

Subcortical retinorecipient targets involved in the image-forming pathway. The dLGN receives direct retinal input and relays that information to V1. Thalamocortical relay neurons in the shell region of dLGN send input to layers 1 and 2/3 of V1, whereas ones in the core region send their axons mainly to layer 4 but also to layers 5b and 6. The dLGN receives direct feedback from corticothalamic neurons in layer 6 of V1 as well as indirect feedback via the TRN. The SC also receives direct retinal input but connects to cortex via intermediate stations such as the LP and the dLGN. Neurons in layer 5 of V1 send feedback to the SC. The LP is connected with both primary and secondary areas of visual cortex. Abbreviations: AL, anterolateral area; AM, anteromedial area; dLGN, dorsal lateral geniculate nucleus; LM, lateromedial area; LP, lateral posterior nucleus; RL, rostrolateral area; SC, superior colliculus; SGS, stratum griseum superficialis; TRN, thalamic reticular nucleus; V1, primary visual cortex.

afferent excitatory input from the cortex. The utility of those cortical projections is not entirely clear, but recent work shows that cortical input to the nucleus of the optic tract—a retinorecipient target in the dorsal brainstem that controls horizontal image-slip compensation—can modulate the gain of this subcortical target under conditions in which multisensory information is ambiguous (Liu et al. 2016). With rare exception (e.g., amygdala), the non-image-forming visual structures that receive cortical projections themselves do not project directly to the cortex, and as

far as we know, none of the retinorecipient targets in the hypothalamus, such as the hypothalamic circadian clock, receive or send connections to the cortex.

In this review, we have elected to focus heavily on the bona fide image-forming visual circuits devoted to sight: the dLGN, SC, and LP/pulvinar and their associated circuits. We do, however, discuss the non-image-forming visual circuits that support sight, because these systems act in concert. Our selection of this emphasis in part reflects space limitations, but it also reflects the fact that other recent publications (Berson 2003, Schmidt et al. 2011) already provided excellent in-depth review of the circuits for light-mediated control of non-image-forming vision.

RETINOTOPIC MAPPING

Image-forming visual areas generally contain complete or near-complete topographic representations of the retinal surface or retinotopic maps. Indeed, the presence of an independent retinotopic map has been informally adopted as a criterion for designating a given brain structure or cortical area as a unique processing station, and this is true regardless of species (Garrett et al. 2014, Marshel et al. 2011, Wang & Burkhalter 2007, Zeki 1993). Retinotopic maps in retinorecipient subcortical visual targets arise from two basic sources: the spatial arrangement of RGC axonal projections in a given retinorecipient target and the spatial extent to which postsynaptic neurons collect synaptic input from those axons (i.e., the degree of axonal convergence).

Retinotopic Maps in the Dorsal Lateral Geniculate Nucleus

As the principal relay of retinal information to the cortex, the dLGN is a key bottleneck for the establishment of conscious sight. Our understanding of retinotopic organization in the mouse dLGN arises mainly from experiments in which focal injections of anterograde tracers were made into different locations in the retina to label the axons of topographically restricted populations of RGCs (Grubb et al. 2003, Métin et al. 1983, Pfeiffenberger et al. 2006, Xu et al. 2011) and from electrode recordings of dLGN neuronal responses to stimuli presented at discrete locations in the visual field (Grubb & Thompson 2003, Piscopo et al. 2013). Studies show that despite housing a relatively even and complete retinotopic map, the mouse's lower visual field is overrepresented in the dLGN (Grubb & Thompson 2003, Piscopo et al. 2013), and subtle anisotropies exist at the boundary of dLGN eye-specific zones (discussed below). Some of these biases may relate to the overall increased density of RGCs in the ventral and nasal portions of the retina (Baden et al. 2016, Bleckert et al. 2014, Dhande & Huberman 2014b, Jeon et al. 1998) or the abovementioned fact that a subset of dLGN-projecting RGC types vary their density and receptive field sizes according to location in the retina (Bleckert et al. 2014; R.N. El-Danaf & A.D. Huberman, submitted manuscript). Regardless, the different RGC types such as direction-selective, center-surround, or contrast-suppressed RGCs that project to the mouse dLGN often terminate in relatively discrete laminar zones (**Figure 2**) (Huberman et al. 2008a, 2009; Rivlin-Etzion et al. 2011; Kay et al. 2011; reviewed in Dhande & Huberman 2014a, Dhande et al. 2015b), each of which contains its own complete retinotopic map. This stacking of retinotopically complete layers is relevant for understanding layer-specific connectivity with the cortex (Bickford et al. 2015, Cruz-Martín et al. 2014; also see below) and likely reflects the progressive accumulation of evolutionarily optimized visual processing streams (Karten & Shimizu 1989, Redies & Puelles 2001). Thus, understanding the connectivity and functional relationships between dLGN, SC, and cortical layers ought to shed light on core principles of visual circuit design in many species.

Electrophysiological recordings from brain slices that measured RGC axon convergence onto individual dLGN neurons suggest that in the mouse, 1–5 RGCs connect to each relay cell (Chen

& Regehr 2000). However, recent studies that used transsynaptic viral tracing from the cortex to the retina (Cruz-Martín et al. 2014, Rompani et al. 2017) or dense electron microscopy (EM) reconstructions of retinogeniculate circuits (Hammer et al. 2015, Morgan et al. 2016) suggest a very different picture: Although some dLGN cells indeed receive retinal drive from small, retinotopically isolated clusters of 1–2 RGC types, other dLGN neurons receive input from large collections (as many as 12–20) of RGCs, within which there are a broad variety of RGC types. These same studies went on to show there are even instances of individual dLGN neurons receiving retinotopically matched input from both eyes (Rompani et al. 2017)—a feature we discuss further in the next section. In summary, there is apparently far more spatial convergence and stimulus-specific integration occurring in the mouse dLGN than one might assume on the basis of older studies and in comparison to what is known for other species. In years to come, it will be important to learn the functional implications of this during natural viewing.

Retinotopic Maps in the Mouse Superior Colliculus

The main task of the SC is to direct head and eye movements to particular locations in visual space. The SC receives direct input from the retina and from visual cortex (**Figures 1** and **3**). In the mouse, ~90% of all RGCs project to the SC (Ellis et al. 2016). This is in stark contrast to the ~10% of RGCs that project to the SC in primates (Perry & Cowey 1984). Retinal inputs to the dLGN and SC of the mouse bear an important relationship: Whereas only ~30–40% of all RGCs project to the dLGN in the mouse (Martin 1986), 100% of the retinogeniculate inputs are collaterals of axons that also innervate the SC (Ellis et al. 2016, Huberman et al. 2008b).

Retinotopic order in the mouse SC arises from a straightforward, two-dimensional–to–two-dimensional (retina-to-SC) mapping, with a 90° rotation of the afferent RGC axons as they enter the SC (**Figure 1**). The main retinorecipient layer of the SC, the stratum griseum superficialis (SGS), contains a representation of the entire contralateral retina (Dräger & Hubel 1976, Koch et al. 2011). The deeper retinorecipient layer in the SC, the stratum opticum (SO), contains a map of the ventrotemporal portion of the ipsilateral eye (Dräger & Hubel 1975) that is in register with the overlying retinal map in the SGS. In terms of outputs, the SC projects to the outer shell portion of the dLGN and to the LP/pulvinar in retinotopic fashion (Bickford et al. 2015, Roth et al. 2016).

Four different approaches each show that the entire contralateral visual field is represented smoothly and completely in the mouse SC (Ackman et al. 2012, Mrsic-Flogel et al. 2005, Xu et al. 2011): (*a*) focal anatomical labeling of RGC axons, (*b*) intrinsic imaging of population SC neuron responses, (*c*) calcium imaging of RGC axons in the SC, and (*d*) calcium imaging of SC neurons (**Figure 4**). The one caveat is that because the density of photoreceptors and RGCs is higher in the nasal and ventral retina, the visual field viewed by those cells—the upper peripheral visual field—has a relatively expanded representation in the caudal SC (Mrsic-Flogel et al. 2005).

Retinotopic Maps in the Lateral Posterior/Pulvinar Nucleus

The pulvinar, referred to as the LP in rodents, is a multimodal thalamic structure that harbors visually responsive cells. One of the main functions of the LP is to relay information about sensorimotor mismatches between self-generated and externally generated visual flow to the cortex (Roth et al. 2016). Anatomical and electrophysiological studies conducted in numerous species indicate the LP/pulvinar has retinotopically organized subdivisions (Allen et al. 2016, Baldwin et al. 2011, Bender 1981, Hutchins & Updyke 1989, Li et al. 2013). Interestingly, the map of elevation in the LP is less pronounced than the azimuth map, but why this anisotropy exists is still

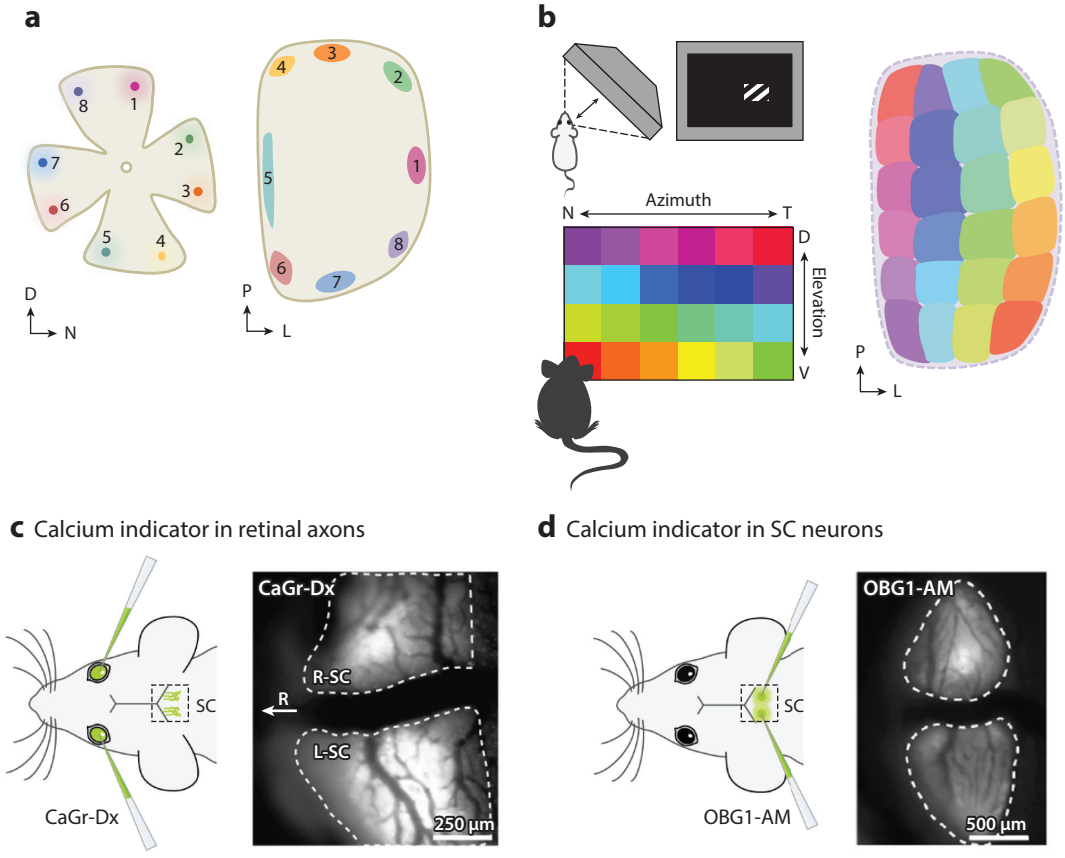


Figure 4

Mapping retinotopy in the SC. (*a*) Focal anatomical labeling of individual RGCs shows the retinotopic order of their axons in SC. Panel adapted from Xu et al. (2011). (*b*) Optical imaging of intrinsic signals in SC is used to map responses to stimuli shown in different positions in visual space. (*c*) Calcium-dye labeling of RGCs allows for two-photon imaging of RGC axons in the SC. (*d*) Bulk loading of a calcium indicator in the SC allows for cellular-level imaging. Panels *c* and *d* adapted from Ackman et al. (2012). Abbreviations: CaGr-Dx, calcium green-1 dextran; D, dorsal; L, lateral; L-SC, left SC; N, nasal; OBG1-AM, Oregon Green 488 BAPTA-1; P, posterior; R-SC, right SC; RGC, retinal ganglion cell; SC, superior colliculus; T, temporal; V, ventral.

unresolved. One idea is that LP is involved in signaling optic flow, which may require expanded representations of the lateral visual fields.

The LP receives direct input from neurons whose cell bodies reside in the deepest portion of superficial SC (Gale & Murphy 2014). The LP also projects in relatively coarse retinotopic fashion to the primary and secondary areas of visual cortex (Roth et al. 2016, Tohmi et al. 2014) (**Figure 5**). In contrast to the dLGN, the LP projects fairly broadly to all cortical layers. That diffuse connectivity, combined with the fact that relay neurons in LP express the calcium-binding protein calbindin, makes this structure analogous to the matrix of thalamic cells that the late Ted Jones (2001) hypothesized acts to modulate cortical states, as opposed to driving analysis of specific sensory information. The LP/pulvinar has also been implicated in modulating attention in primates (Saalmann et al. 2012), but comparable recordings from LP during attention tasks or causal tests of this hypothesis in the mouse are still lacking. There is increasing interest in

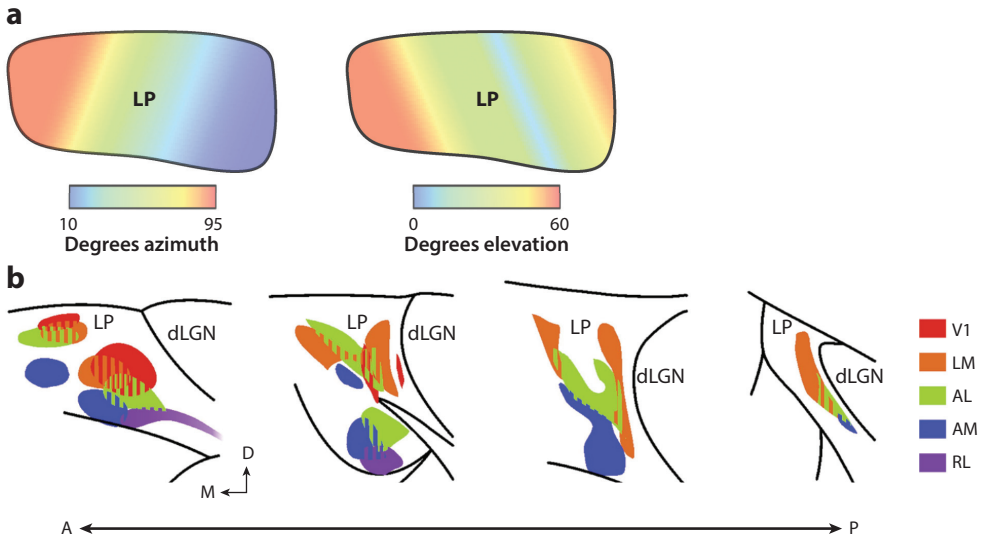


Figure 5

Topographic organization of the LP. (*a*) Vertical and horizontal retinotopy in the LP. Panel adapted from Allen et al. (2016). (*b*) Organization of connections with V1 and extrastriate visual areas in the LP. Panel adapted from Tohmi et al. (2014). Abbreviations: A, anterior; AL, anterolateral area; AM, anteromedial area; D, dorsal; dLGN, dorsal lateral geniculate nucleus; LM, lateromedial area; LP, lateral posterior nucleus; M, medial; P, posterior; RL, rostrolateral area; V1, primary visual cortex.

understanding LP-cortical function both for the sake of understanding its role in vision and for probing nonprincipal relays to cortex in sensory processing. We anticipate much of that work will take place in the context of the visual LP in the mouse.

Retinotopic Maps in the Visual Cortex

According to the criterion that a visual cortical area is one containing a distinct map of retinotopic space (Zeki 1978), as many as 11 distinct visual cortical areas have been identified in the mouse using anatomical and physiological methods (Garrett et al. 2014, Wang & Burkhalter 2007). In a now classic study, Wang & Burkhalter (2007) carried out triple-color anterograde and retrograde labeling from primary visual cortex (V1) and observed retinotopically correspondent patches of label in 8 other cortical regions, thus indicating the presence of 9 total visual cortical areas, each with a different size and shape and receiving reciprocal connections with V1. Wide-field imaging of intrinsic hemodynamic responses or of calcium signals confirmed those findings and expanded on them by revealing that (*a*) each cortical area best responds to a specific category of visual stimuli (e.g., speed, direction) and (*b*) there are two additional retinotopically complete areas. This brings the current count of the total number of visual cortical areas in the mouse to 11 (Garrett et al. 2014) (**Figure 6**).

Interestingly, the imaging studies of Garrett et al. (2014) reported that the V1 retinotopic map represents a vastly greater portion of the visual field than do any of the extrastriate visual areas. However, the extrastriate retinotopic maps do not simply contain fragmented representations of the larger retinotopic space; rather, they contain complete maps of the retinal surface that are warped to dramatically overrepresent specific locations in the visual field and are optimized for processing specific types of visual feature information (**Figure 6**). In the future, it will be important

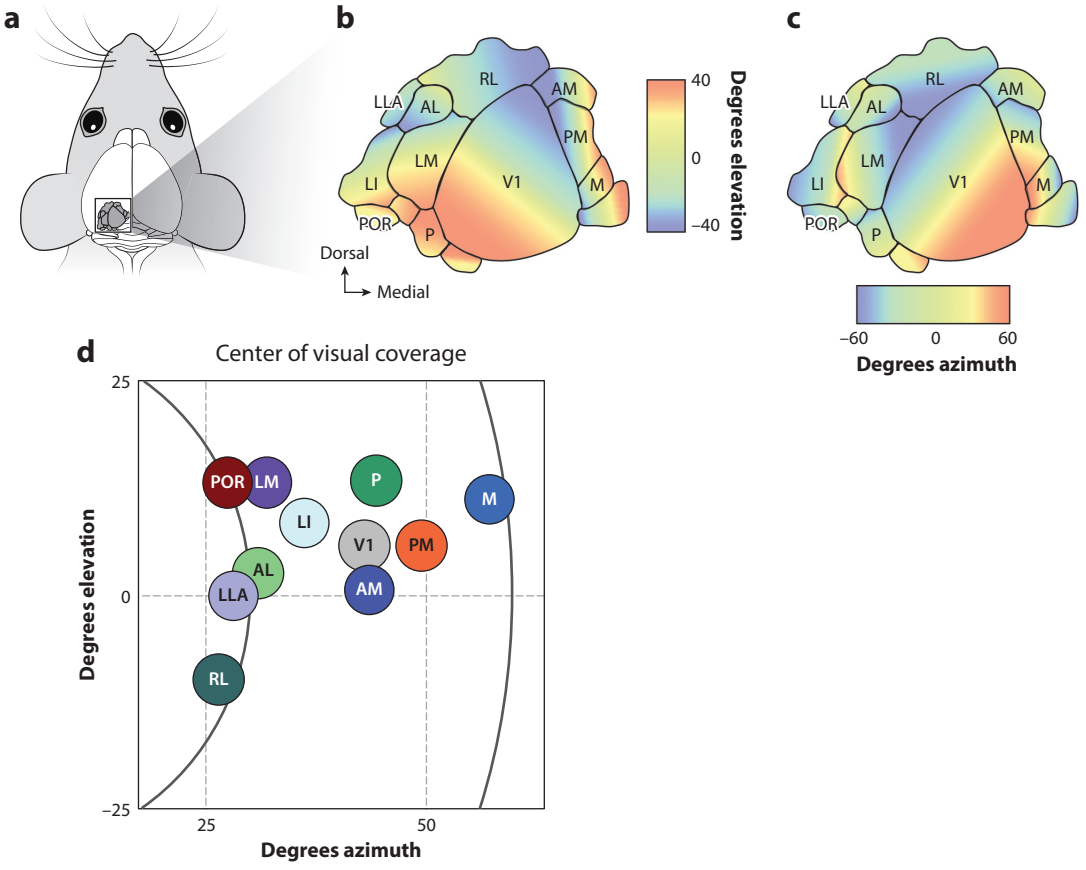


Figure 6

Retinotopy of visual cortical areas. (*a*) Location of visual cortical areas in the mouse. (*b*) Vertical and (*c*) horizontal retinotopy in visual cortical areas. (*d*) Visual field coverage in different visual cortical areas. Panels *b–d* adapted from Garrett et al. (2014). Abbreviations: AL, anterolateral area; AM, anteromedial area; LI, laterointermediate area; LLA, laterolateral anterior area; LM, lateromedial area; M, medial area; P, posterior area; PM, posteromedial area; POR, postrhinal area; RL, rostrolateral area; V1, primary visual cortex.

to understand if and how the patterns of connectivity arising from the dLGN-to-V1 and from the V1-to-extrastriate areas relate to these map specializations or hot spots. It will also be crucial to consider how input from structures such as the LP contributes to these map specializations. The ethological significance of these partial and apparently highly specialized maps currently remains unknown, but the growing number of visual behavioral assays labs have developed for the mouse (e.g., Busse et al. 2011, De Franceschi et al. 2016, Dhande et al. 2013, Glickfeld et al. 2013b, Hoy et al. 2016, Yilmaz & Meister 2013) lend themselves nicely to working out the answer to this important issue.

EYE-SPECIFIC AND BINOCULAR MAPS

The eyes of the mouse are positioned somewhat laterally within its skull (**Figure 7**). As a consequence, each eye views largely nonoverlapping portions of the visual scene. Both eyes do, however, view the same central 40° of visual space, enabling the enhanced depth perception associated with

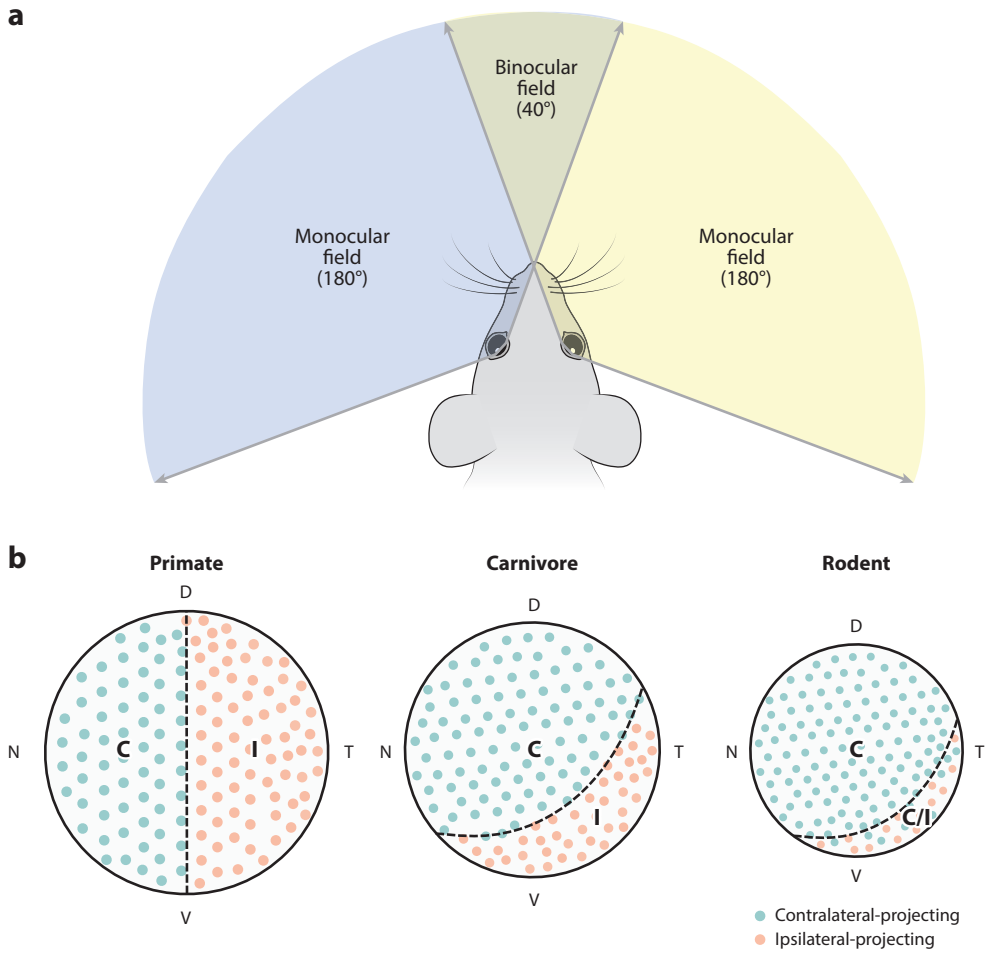


Figure 7

Binocularity in the mouse. (*a*) The lateral eye position of the mouse results in each eye viewing largely nonoverlapping regions of the visual scene (monocular field). Both eyes view the central 40° of visual space, providing some degree of stereopsis (binocular field). (*b*) Organization of contralateral-projecting (*blue*) and ipsilateral-projecting (*pink*) retinal ganglion cells in the primate, carnivore, and rodent retinas. Abbreviations: C, contralateral-projecting; D, dorsal; I, ipsilateral-projecting; N, nasal; T, temporal; V, ventral.

stereopsis (**Figure 7**). Rats have been proposed to preferentially view the overhead visual fields through the use of convergent upward rotations of the eyes (Wallace et al. 2013), but that result has been challenged (Meister & Cox 2013), and how mice view different portions of the visual field as they move and according to their eye movements needs careful analysis.

Carnivores and primates have a strict line of decussation for RGCs, meaning that the cell bodies of the RGCs that project contralaterally into the brain reside in a distinct retinotopic portion of the eye from those which project ipsilaterally. In the mouse, the situation is quite different: There is no true line of decussation because RGCs from throughout the entire retina project to the contralateral hemisphere, and the small proportion of RGCs that project to the ipsilateral brain hemisphere (approximately 5%) are interspersed among the contralateral-projecting RGCs within

the ventrotemporal retina (**Figure 6**) (Dräger & Olsen 1980, Herrera et al. 2003, Koch et al. 2011, Petros et al. 2008).

As a field, we still do not know (*a*) which RGC types comprise the ipsilateral-projecting population and (*b*) which of those ipsilateral-projecting RGC types connect to the dLGN and SC. To thoroughly understand visual processing in V1 as well as other aspects of vision in this species, these issues need resolution. Mice that selectively express Cre in the ipsilateral-projecting RGC population (e.g., Koch et al. 2011) will no doubt be helpful in resolving this. What is clear is that in mice older than postnatal day 12 (P12), axonal projections from the two eyes are segregated into distinct domains within all the retinorecipient targets that receive binocular input—a process that arises during development and that we discuss in detail below and in previous reviews (Huberman et al. 2008a) (**Figure 1**). Next, we review the architecture and functional implications of this eye-specific segregation in the dLGN and SC and in downstream targets such as V1.

Ocular Maps in the Dorsal Lateral Geniculate Nucleus

The trajectories and termination zones of RGC projections from each of the two eyes can be visualized simultaneously by labeling each retina with different color tracers, such as cholera toxin conjugated to green- or red-fluorescing fluorophores (Huberman et al. 2003, Jaubert-Miazza et al. 2005, Luo et al. 2013, Muir-Robinson et al. 2002, Stellwagen & Shatz 2002). Axons of ipsilateral-projecting RGCs project to a restricted domain in the dorsomedial dLGN, where they are segregated from RGC axons arising from the contralateral eye (**Figure 1**) (Muir-Robinson et al. 2002), which corroborates evidence from single-eye labeling studies (Godement et al. 1984, Huh et al. 2000). From the postsynaptic perspective, ocularity can be measured using single-unit or patch electrodes from target neurons to determine if they sample and receive synaptic input from one or both eyes (Grubb & Thompson 2003, Howarth et al. 2014). Anatomically distinct eye-specific layers separated by interlaminar zones are present in the carnivore and primate dLGN but are absent in the mouse (**Figure 8**), raising questions as to whether mouse dLGN neurons

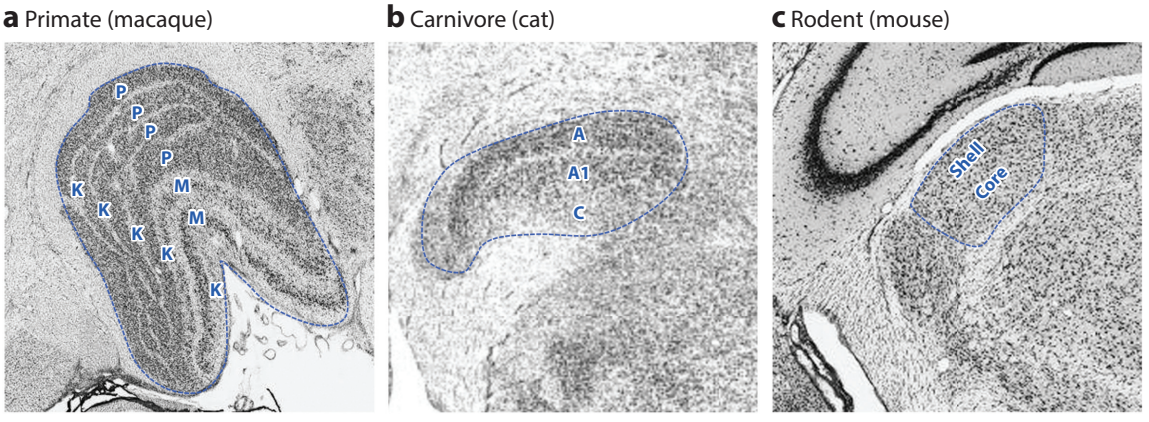


Figure 8

Cytoarchitectural structure of the dorsal lateral geniculate nucleus (dLGN) in different species. The dLGN of primates and carnivores such as cats and ferrets have clear cellular layers separated by intralaminar zones. However, the cellular structure of the dLGN in the mouse is homogeneous and does not have any obvious lamination. Images from **http://BrainMaps.org**. Abbreviations: K, koniocellular; M, magnocellular; P, parvocellular.

have dendritic territories limited to eye-specific domains. Most experiments report that dLGN neurons of the mature mouse are driven functionally by RGCs from one or the other eye but not both—a feature that emerges during development (see below) (Grubb et al. 2003, Jaubert-Miazza et al. 2005, Zhao et al. 2013) and is consistent with features of the dLGN in carnivores and primates (Hubel & Wiesel 1961). However, recent reports suggest that the dLGN of the mouse, unlike other species, contains an abundance of binocularly innervated cells (Howarth et al. 2014, Rompani et al. 2017). The functional implications of this for cortical processing, and for visual perception, await resolution.

Ocular Maps in the Superior Colliculus

In the SC, RGC axons from the ipsilateral retina project to the rostromedial portion of the deeper SO layer and therein are segregated from contralateral eye axons in the rostromedial SC (**Figure 1**) (Dräger & Olsen 1980, Godement et al. 1984, Haustead et al. 2008, Xu et al. 2011). Comparatively little is known about the function of this binocular representation, but recent evidence shows that RGC convergence, synaptic strength, and maturation vary with SC mediolateral position (Furman & Crair 2012, Furman et al. 2013), implying that binocular and monocular regions of the SC process and incorporate visual signals differently.

Ocular Maps in the Visual Cortex

Few structure-function relationships have occupied the minds and efforts of neuroscientists more than the brain circuits for binocular vision. Ocular dominance columns (ODCs)—the cortical feature discovered and made famous by Hubel & Wiesel (1969) in their classic studies of cat and primate V1—represent alternating patches of right eye–dominated and left eye–dominated cortical territories. ODCs are most prominent and most famously elucidated as stripes when viewed tangentially (from the dorsal surface) in layer 4 of primate V1. In carnivores, ODCs are more patchy than stripe-like but are nonetheless still quite prominent, whereas in the mouse, owing to the rather limited ipsilateral RGC projection to the dLGN and binocular field of view, geniculocortical projections do not segregate into anatomical ocular dominance stripes or patches. Instead there is a single binocular zone that receives mixed input from both the ipsilateral and contralateral eyes. Thus, purely ipsilateral eye–driven cells are very rare in the mouse cortex (Dräger 1975). Ten-m3 mutant mice, which have an altered dLGN ipsilateral topography and an expanded ipsilateral projection from dLGN to visual cortex, do have ODCs (Merlin et al. 2013), supporting the idea that this feature is indeed the reflection of the degree of ipsilateral eye territory in the dLGN. However, recent evidence demonstrates the existence of robust ODCs in the rat—a species that also has limited ipsilateral RGC projections (Laing et al. 2015). This raises the intriguing possibility that the absence of ODCs in mice could reflect the presence of the numerous binocularly innervated cells in the dLGN (Howarth et al. 2014, Rompani et al. 2017). Going forward, it will be useful to obtain more detailed maps of eye-specific and binocular retinogeniculocortical connectivity in the mouse. The current transsynaptic viral tracing methods such as modified rabies make it possible to link retinal, dLGN, and V1 circuitries in detail (e.g., Callaway & Luo 2015, Cruz-Martín et al. 2014, Rompani et al. 2017). Thoughtful comparison of those features with functional attributes of the mouse dLGN (e.g., Piscopo et al. 2013) are needed to achieve full understanding of these important aspects of visual circuitries, and ideally, those features will be placed within the context of mouse visual behaviors that rely on binocular vision.

FUNCTIONALLY DISTINCT PROCESSING STREAMS AND CIRCUITRIES

The retinotopic and eye-specific maps described above represent evolution's decision as to how to best represent the topography of visual space through the two eyes. However, within those spatial maps, specific features of the visual world must also be represented. Such features include motion, direction, colors, and contrast. Visual feature representation is accomplished primarily in two ways: (*a*) Neurons can either connect to distinct overall targets, or (*b*) they can connect to distinct locations within each target. Generally, they do both. A consistent scheme for processing select visual features, often referred to as parallel processing, is the subdivision of target nuclei into layers—each of which receives afferent input (axons and synapses) carrying distinct qualities of visual information.

In the mouse, parallel processing of unique visual features starts as early as the rod-cone distinction, but the first anatomically obvious parallel pathways are the termination patterns of the axons arising from the 33 functionally defined RGC subtypes (Baden et al. 2016). As mentioned above, each of those RGC subtypes responds best to a particular feature in the visual world and connects to anywhere from 1–4 separate subcortical visual areas through direct projections and axon collaterals (Dhande et al. 2011, 2015b; Huberman et al. 2008b). Then, within many of those targets—most notably the dLGN and SC—the axons of different categories of RGC types are arranged into distinct layers. Coupled with the laminar-specific arrangement of target neuron cell bodies, dendrites, or both, discrete modules across the depth of the dLGN and SC for processing different visual features arise for all locations in the retinotopic map (**Figure 2**).

Layered Functional Channels in the Retinogeniculocortical Pathway

The mouse dLGN harbors layers, but they are more cryptic than those found in other species such as macaques or cats. For example, the cytoarchitectonic structure of mouse dLGN appears homogeneous—it lacks the overt cellular layers separated by intralaminar zones seen in carnivores and primates (**Figure 8**). Inspection with the appropriate methods reveals, however, that the rodent dLGN does in fact possess functionally distinct layers related to the unique termination patterns of functionally distinct categories of retinogeniculate projections (Martin 1986, Reese 1988). Experiments in mice with genetically tagged RGC subtypes revealed that alpha-like RGCs connect to the central core region of the dLGN, whereas bistratified On-Off direction-selective RGCs connect to a shell region that resides adjacent to the optic tract, as do an Off type of monostratified direction-selective ganglion cells (DSGCs) termed J RGCs (Ecker et al. 2010; Huberman et al. 2008b, 2009; Kay et al. 2011; Kim et al. 2008, 2010; Rivlin-Etzion et al. 2011) (**Figures 2** and **9**). The thalamic neurons in each of these two dLGN regions appear to differ as well. Y-like and X-like dLGN relay neurons predominate in the core, whereas W-like dLGN neurons prevail in the shell (Krahe et al. 2011) (**Figures 2** and **9**). Like other species, the dLGN of the mouse also contains intrinsic interneurons. In the mouse, they are relatively evenly distributed throughout the entire dLGN; however, it is still unclear whether different subtypes exist (Seabrook et al. 2013b). Moreover, these interneurons have extensive, highly complex dendritic processes, which can cross eye-specific borders and the functionally distinct layers in dLGN (Seabrook et al. 2013b).

The layers of RGC input and distinct neuron types situated within each laminar termination zone translate to distinct thalamocortical output circuits as well. In the shell region of the dLGN, On-Off DSGCs and Off-DSGCs synapse onto neurons with hemispheric (W-like) dendritic fields, which in turn project to layers 1 and 2/3 of V1 (Bickford et al. 2015, Cruz-Martín et al. 2014,

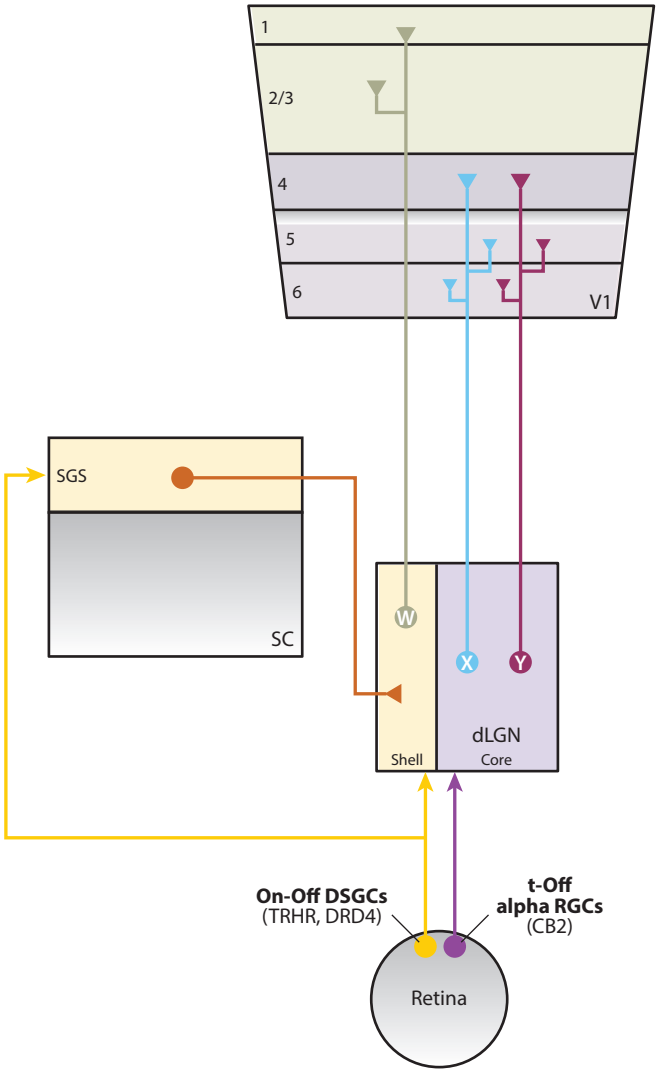


Figure 9

Input and output of the dLGN of the mouse. X-like and Y-like relay cells reside in the core region of the dLGN, receive input from alpha RGCs, and project their axons mainly to layer 4 of V1. The dorsolateral or shell region of the dLGN contains W-like relay cells, which receive retinal input from On-Off DSGCs and input from the SC. These cells in turn send their axons to layers 1 and 2/3 of V1. Abbreviations: CB2, calbindin 2; dLGN, dorsal lateral geniculate nucleus; DRD4, dopamine receptor 4; DSGC, direction-selective ganglion cell; RGC, retinal ganglion cell; SC, superior colliculus; SGS, stratum griseum superficialis; TRHR, thyrotropin-releasing hormone receptor; V1, primary visual cortex.

Krahe et al. 2011). By contrast, biconical (X-like) and symmetrical (Y-like) dendritic fields are thought to receive input from non-direction-selective alpha-like RGCs and send their axons to layer 4 of V1 (**Figure 9**). The implications of this are several, but from a circuit design standpoint, they point to the idea that the mouse retino-dLGN-V1 circuit—although lacking conspicuous cellular lamination—nonetheless has parallel pathway components that incorporate cell type–specific laminar terminations, in a manner quite similar to that found in other species.

Collicular Inputs to the Dorsal Lateral Geniculate Nucleus

Interestingly, neurons in the dLGN shell receive topographically organized input from neurons in the SGS of the SC, but whether the SC to dLGN connections arise from retinorecipient neurons in the SC or a different category of SC cells remains unclear (Bickford et al. 2015) (**Figures 2** and **9**). Regardless, this specific pattern of SC to dLGN shell input sets up a closed-loop network for directional processing that possibly influences how cells at each station—dLGN, SC, and V1—respond to moving visual stimuli, including object versus background motion (Bickford et al. 2015, Roth et al. 2016).

The sublayers of the SC (upper SGS, lower SGS, and SO) can also be defined by the signature patterns of inputs arising from specific classes of RGCs (Dhande & Huberman 2014a; Dräger & Hubel 1976; Hong et al. 2011; Huberman et al. 2008b, 2009). SC neurons normally are not selective with respect to On or Off properties; that is, most SC cells are On-Off and respond to both the onset and offset of a light stimulus (Chandrasekaran et al. 2007, Inayat et al. 2015). Because cells outside the shell portion of the mouse dLGN are mostly tuned for On or Off but not both, and all inputs to the dLGN represent collaterals of RGC axons that also project to the SC, the abundance of On-Off responses in the SC therefore must be the consequence of SC neuron dendrites collecting inputs from many types of RGCs, and indeed the receptive field structure of SC neurons and intracellular fills of SC neurons in the mouse support that idea (Chandrasekaran et al. 2007, Gale & Murphy 2014).

Homology of Retinogeniculocortical Circuits in Mouse, Carnivores, and Primates

An interesting consideration is the high degree of similarity between the circuitry and neurochemical attributes of mouse dLGN shell (where On-Off DSGC inputs prevail) and the SGS layer of the SC. These include calbinidin immunoreactivity, small W-like cells, and sluggish (low axon-conduction velocity) On-Off retinal inputs (Grubb & Thompson 2004, Huberman et al. 2009, Stone 2013). Moreover, the dLGN shell also bears striking afferent and neurochemical resemblance to the so-called C-layer pathways in carnivores and the koniocellular pathways in primates, raising the possibility that the C-layer and koniocellular pathways—most well known for carrying yellow-blue opponent signals—may be responsible for processing direction- and/or orientation-selective information. Indeed, recordings from neurons in the K layers of the marmoset and other primates revealed direction- and orientation-selective properties in the koniocellular pathways (Cheong et al. 2013, White et al. 2001, Xu et al. 2002), and such responses are also found in the human dLGN by fMRI (Ling et al. 2015).

Orientation and Direction Selectivity

The detection of complex features within a visual scene, such as perception of motion, was initially thought to be a signature property of visual cortex. However, recent studies demonstrate that processing of this type of visual information occurs long before it is transmitted to higher visual areas. There is now considerable evidence that subcortical areas—for instance, the dLGN—contain neurons sensitive to direction or orientation that could bias the tuning seen in visual cortex. Below, we discuss how information about the direction or orientation of movement is passed along the visual pathway.

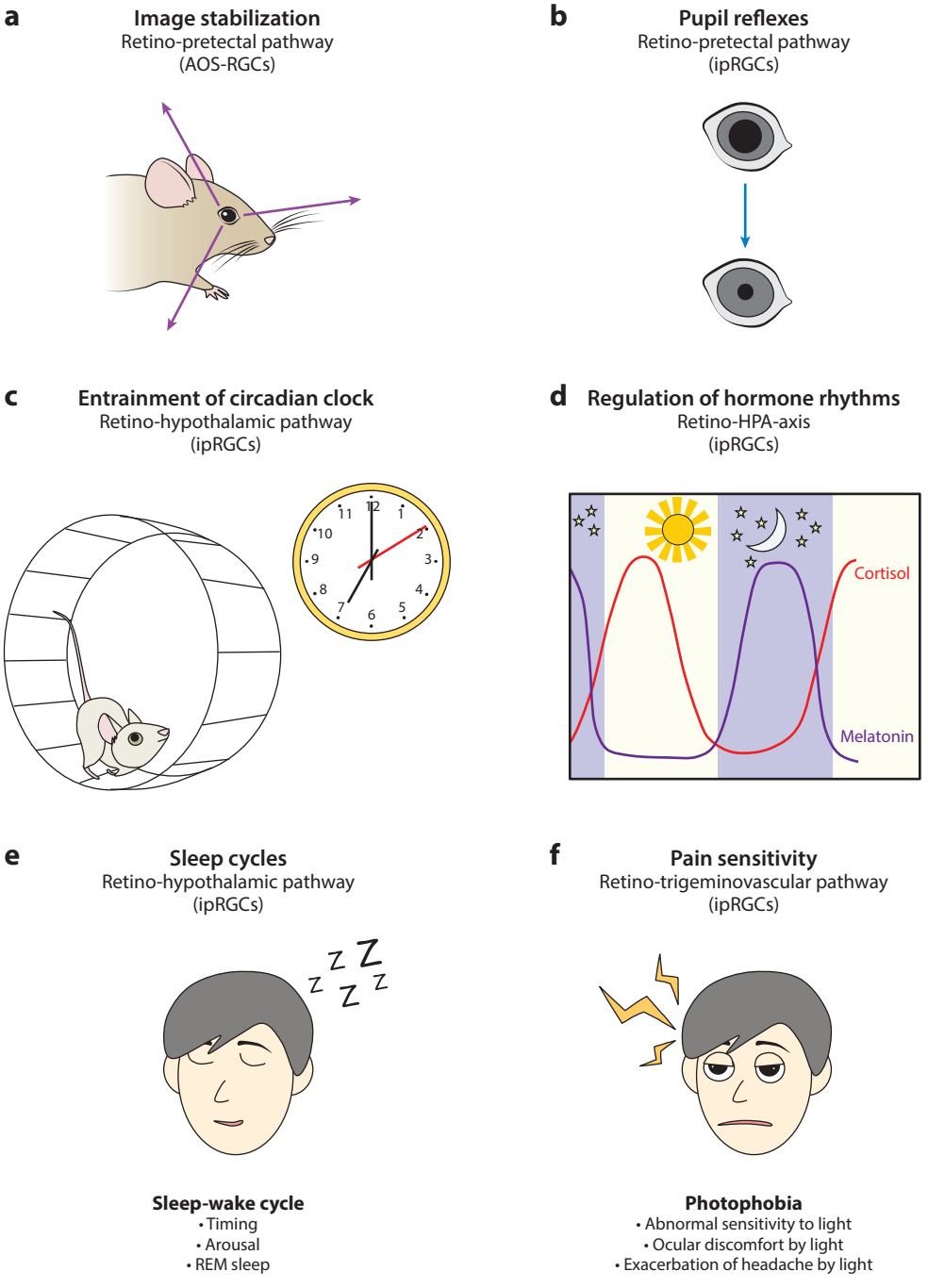
In dorsal lateral geniculate nucleus and retinogeniculocortical circuits. Primary receptive neurons in the mouse visual system (as in multiple other mammalian models) respond preferentially to both simple center-surround stimulation at early (retinal and dLGN) levels of processing and visual stimuli that move in either single polar directions (direction-selective) or in two polar-opposing directions (orientation-selective, usually at later processing stages). In the mouse retina, direction selectivity shows up first in genetically defined populations of RGCs that respond preferentially to one of the four cardinal directions (Briggman et al. 2011, Huberman et al. 2009, Wei et al. 2011). This information is passed to the dLGN shell, in which direction selectivity is either maintained or sharpened or DSGC inputs are combined to generate orientation-selective cells (Cruz-Martín et al. 2014, Marshel et al. 2012, Scholl et al. 2013). Interestingly, researchers have also demonstrated recently that some mouse RGCs are orientation selective (Baden et al. 2016, Nath & Schwartz 2016). Thus, neurons in the dLGN that are orientation selective may acquire that property directly from the retina (Zhao et al. 2013).

An exciting new area of focus that grew largely out of the genetic and imaging tools available in the mouse is the issue of how dLGN receptive fields are maintained, transformed, or both as they pass to cortex. This issue has long been addressed in cats and primates, but from the general framework that the dLGN-projecting RGCs and dLGN mainly contain center-surround units (spot detectors) and that the properties of direction and orientation selectivity show up first in V1. However, the presence of On-Off and Off DSGCs and orientation-selective RGCs that project to the dLGN in the mouse and the fact that many dLGN neurons in the shell are direction and/or orientation selective (Dhande & Huberman 2014a, Piscopo et al. 2013) promoted the exploration of whether these properties are conferred onto the cortex from subcortical structures. Retrograde transsynaptic labeling of V1-dLGN RGCs from various depths of V1 layers revealed, for example, that On-Off DSGCs project to W-like cells in the dLGN shell that, in turn, project to superficial V1 and thereby deliver direction- and orientation-selective information to V1 (Cruz-Martín et al. 2014). Cruz-Martín et al. also showed that spot-detector center-surround RGCs project to the dLGN core and that the X- and Y-like cells in the dLGN core project to deeper layers 4 and 5b of V1, consistent with the classic model of retinogeniculocortical connectivity (Alonso et al. 2001, Hubel & Wiesel 1972, Usrey et al. 2000). Those findings raised two questions: What is the functional purpose of the direction- and orientation-selective retinogeniculocortical pathway that bypasses layer 4? And are there equivalent circuits for communicating direction- and orientation-selective information from the thalamus directly to cortex in other species?

The answer to the first question is now more or less complete. The bulk of evidence—both anatomical and electrophysiological evidence with imaging and electrode recordings—shows that, indeed, direction- and orientation-selective information to the shell is relayed to superficial V1 (Bickford et al. 2015, Cruz-Martín et al. 2014, Kondo & Ohki 2016, Piscopo 2013), whereas neurons in the core region of the dLGN project to deeper layers of V1 (Bickford et al. 2015, Cruz-Martín et al. 2014, Lien & Scanziani 2013). Elegant work from the Roska lab showed recently that selective deletion of retinal direction selectivity causes a marked reduction in direction-selective tuning of neurons in superficial V1, whereas receptive fields of neurons in deeper V1 layers is relatively unchanged by loss of retinal direction selectivity (Hillier et al. 2014).

In regards to the second question of whether equivalent circuits exist in other species, it is interesting to note that in every species in which this has been examined—mouse (Cruz-Martín et al. 2014), rat (Martin 1986), tree shrew (Usrey et al. 1992), rabbits (Swadlow & Weyand 1985), ferret (Erisir & Dreusicke 2005), and macaque (Lund et al. 1975)—there is a dLGN projection arising from neurons in layers close to the optic tract (shell in the mouse, C-layers in carnivores and shrews, and K-layers in primates) that bypasses layer 4 and projects to the more superficial

layers 1–3 of V1. Moreover, in so many ways, this projection system resembles pulvinar projections to V1: neurochemically, morphologically, and with regard to cell types (**Figure 10**). Parsing the functional significance of these two parallel projection systems for visual perception and behavior represents one of the major goals for the field in the years to come. Collectively, these findings also underscore the extent to which tools and detailed study of the mouse visual system are revealing



more general themes about the organization of visual circuits in other species and, thus, driving new research directions in those models as well. For example, the search for On-Off DSGCs in tree shrews and primates is now under way (Dhande et al. 2015a; G. Field & D. Fitzpatrick, personal communication).

Orientation selectivity in the mouse V1. Unlike in cats and monkeys, orientation-selective neurons in V1 follow no clear pattern in relationship to one another across the retinal surface, instead showing a so-called salt and pepper organization. Recent work that did functional imaging of secondary visual areas in cortex has shown that responses in V1 neurons to visual signals are divided by function into separate pathways for action guidance and shape recognition (Glickfeld et al. 2013a, 2014), similar to the primate dorsal and ventral streams, but comparable characterization of the nine strongly retinotopically connected secondary visual cortical areas (Wang & Burkhalter 2007) is still in its early stages.

Orientation selectivity in the mouse superior colliculus. Recently, orientation-specific maps were reported in the SC that have relatively large swaths of retinotopic space overrepresenting specific orientations (Ahmadlou & Heimel 2015, Feinberg & Meister 2015). This is curious for two reasons: (*a*) Previously, orientation selectivity was thought to arise within the cortex but not to exist in subcortical structures (but see L. Wang et al. 2010); and (*b*) the maps described do not represent all orientations evenly. The specific utility of these orientation hot spots for head movement, eye movement, or other behaviors remains unclear at this time (Ahmadlou & Heimel 2015, Feinberg & Meister 2015, Inayat et al. 2015).

Visuomotor and Multimodal Context-Dependent Processing

An important function of the mouse visual system is the rapid estimate of relative movement and speed that allows successful integration with movement. To this end, recent reports demonstrated that locomotion had significant modulation of visual sensory responses in V1, a surprisingly early level of visual processing for sensorimotor integration (Niell & Stryker 2010). Similarly, auditory signals have also been found to affect neuronal response properties and tuning in V1 (Ibrahim et al. 2016, Iurilli et al. 2012), modifying the assumption that mouse V1 serves primarily as a simple entry point for visual signals into the cortex. There is rapidly growing interest into how these

Figure 10

Behavioral output of non-image-forming visual pathways. (*a*) Axons of AOS RGCs in brainstem (NOT and MTN) are involved in the pathway, generating head and eye movements to compensate for retinal slip and provide image stabilization. (*b*) ipRGCs mediate the pupillary light reflex or reflexive response of constricting the pupil to increases in luminance via the OPN. (*c*) ipRGCs that project to the SCN in the hypothalamus are essential for the entrainment of internal biological clock rhythms to external cues such as the light-dark cycle. (*d*) ipRGCs sending information about external cues can also influence the HPA axis to regulate the rhythm of hormones. The secretion of these hormones can affect physiological mechanisms such as sleep and stress. (*e*) ipRGCs going to the hypothalamus have also been implicated in the regulation of sleep. (*f*) Migraines are typically associated with photophobia, such as abnormal sensitivity to light, ocular discomfort, and exacerbation of headache by light. Signals transferred by ipRGCs to thalamus and pretectum are integrated into the trigeminovascular pathway and result in a nociceptive response to light.
Abbreviations: AOS, accessory optic system; HPA, hypothalamic-pituitary-adrenal; ipRGC, intrinsically photosensitive RGC; MTN, medial terminal nucleus; NOT, nucleus of the optic tract; OPN, olivary pretectal nucleus; REM, rapid eye movement; RGC, retinal ganglion cell; SCN, suprachiasmatic nucleus.

multimodal and context-dependent operations of the visual pathway take place. Next, we consider the behavioral paradigms that enable probing of the basic and context-dependent operations of the visual cells, circuits, and pathways discussed above.

VISUALLY DRIVEN BEHAVIORS

Predator Aversion

The mouse displays innate defensive behaviors, which are essential for avoiding predators and thus for survival. In nature, mice often fall prey to aerial predators, such as hawks and owls. Behavioral analyses using a looming stimulus—an expanding dark disc shown on a monitor placed atop an arena—can mimic the appearance of an approaching predator from above (Yilmaz & Meister 2013). In the mouse, this triggers either freezing for an extended period of time or escaping an open area for cover under a shelter (Yilmaz & Meister 2013). Incredibly, a light expanding disk or an expanding disk presented below the animal has no impact on freezing or flight, indicating that a location in the visual field and the specific nature of the stimulus presented there are firmly represented in the visual system and linked to defined motor command circuitry. In multiple species, the SC or its nonmammalian homolog, the optic tectum, plays a role in mediating this behavior (Ingle 1973, Shang et al. 2015, Temizer et al. 2015, Wei et al. 2015, Westby et al. 1990).

Electrophysiological recordings as well as activity-dependent c-*Fos* expression demonstrate that neurons in superficial SC are active during looming stimuli (Wei et al. 2015, Zhao et al. 2014). The cell types and subcortical connections involved are also becoming clearer from experiments using optogenetic approaches, monitoring of activity-related immediate early genes, and Fos-TRAPing (Guenthner et al. 2013), in which the loom-activated Fos+ cells turn on Cre during the loom/fear experience and can then be replayed or inactivated using Cre-dependent activity manipulations (Shang et al. 2015, Wei et al. 2015). A pathway between glutamatergic neurons located in medial SC and the basolateral complex of amygdala, possibly via LP, may mediate the freezing response to a looming stimulus (Wei et al. 2015). Excitatory parvalbumin-positive neurons in the SC connect to the amygdala through the parabigeminal nucleus in the brainstem and can trigger fear responses to looming stimuli (Shang et al. 2015).

A recent study also found evidence that distinct defensive responses are evoked by selective features of visual cues that mimic the presence of a predator, with looming stimuli producing fleeing behavior, whereas sweep stimuli induce a freezing response in the mouse (De Franceschi et al. 2016). The sweep stimulus mimics a distal threat, so freezing may be more advantageous to avoid detection by an incoming predator. Whether these different defensive strategies are mediated through distinct visual pathways remains to be determined, but these pathways should be decipherable using the *Fos*-TRAP or similar technologies described above.

Visual Hunting and Prey Capture

Surprisingly, rodents also capture and feed on various prey, such as insects or even small mammals, reptiles, and amphibian species. In fact, one mouse species—the northern grasshopper mouse—relies almost solely on predation for survival (Langley 1989). A recent report described the prey capture behavior of the common laboratory mouse in quantitative detail and found that laboratory-bred mice captured and fed on insects (grasshoppers) readily within a short time frame (Hoy et al. 2016). They further reported that vision accounted for the majority of long-range prey detection and accurate prey-stalking and approach behavior. This finding demonstrates a heretofore largely ignored but ethologically relevant visual behavior in the mouse that should allow for the

investigation of a complex behavior with genetic access to the underlying circuit architecture. An interesting question is whether the mouse used vergence eye movements and/or the binocular portion of their visual fields selectively to hunt, as other species such as carnivores and zebrafish do (Bianco et al. 2011). Brain imaging and real-time eye tracking of freely moving animals should be able to resolve this (Flusberg et al. 2008).

Visual Cliff and Depth Perception

For most terrestrial animals, including the mouse, falling from a high location can have hazardous consequences, and thus the ability to visually discriminate the relative depth of surfaces from one another has a significant impact on survival implications. At the same time, mice are impressive gymnasts, routinely climbing up and down near-sheer surfaces to forage and socialize. In both these contexts, depth perception and selective decisions about whether to take or avoid particular trajectories are paramount. Binocular disparity, or the positional difference of a given point in space seen by each eye, contributes critically to the perception of depth. In species with forward-facing eyes, visual fields overlap almost totally, allowing them to perform stereoscopic depth discrimination, but the laterally placed eyes of the mouse make depth perception more problematic using only their small degree of binocular overlap (**Figure 7**).

The visual cliff test takes advantage of the innate aversion to heights that humans and other animals possess and that can be used to probe an animals' ability to discriminate depth (Walk & Gibson 1961). In a modified visual cliff test for rodents, high-contrast checkerboard patterns placed at different distances below a piece of clear acrylic or glass create the illusion of a shallow safe side and a deeper cliff/danger side (Fox 1965). If mice are placed on a platform or ledge between these two sides, they tend to step down onto the shallow side—a choice that is visually guided because cues from other sensations, such as whisking and olfaction, are not available in this regime. Moreover, mice with rod deficiency or retinal degeneration no longer exhibit a shallow-side preference but instead choose randomly from either side, indicating that vision mediates this choice (de Lima et al. 2012, Fox 1965, Frank & Kenton 1966, Lim et al. 2016, Nagy & Misanin 1970). Disruption of the ipsilateral retinal projections to dLGN can interfere with the normal cliff response, showing the importance of the retinogeniculocortical pathway and binocularity therein (Leamey et al. 2007). This has been demonstrated most clearly by genetic knockout of Ten-m3, an adhesion molecule expressed by RGCs, which results in mistargeting of RGC axons from the ipsilateral eye to dLGN, creating an elongated ipsilateral zone along the dorsomedial-ventrolateral axis (Leamey et al. 2007). One functional consequence of this mismatch of retinal projections in the dLGN is alteration of visual signal transfer to visual cortex and loss of a cohesive map of binocular visual space. One idea is that such mismatch leads to interocular suppression similar to that seen in Siamese cats or in strabismic primates (Leamey et al. 2007, Merlin et al. 2013).

ASSEMBLY OF THE MOUSE VISUAL SYSTEM

Mouse visual circuit development is governed by the cooperative influence of genes, molecular factors, and neuronal activity. The relevant activity may be generated spontaneously (without sensory drive) or by visual stimulation. After visual neurons are born, are specified, and migrate into position, they extend out processes to form circuit connections within and between targets. At the earliest stages of neurite outgrowth, axon pathfinding and target selection are driven primarily by molecular guidance cues that act as intermediate signposts to steer one direction or another. Once they reach the proximity of their targets, they must match to them in a process that involves both positive ("go here") and negative ("don't go there") signals. Visual afferents then must select the

appropriate region, layer, and cells within that target structure. Synaptogenesis and synapse elimination coincide with these later steps (Cheng et al. 2010, Josten & Huberman 2010). Later stages of circuit development are more heavily influenced by spontaneous and sensory-evoked activity to drive the strengthening, consolidation, and refinement of existing within-target circuitry, often by employing molecular signals and physical recruitment of nonneural cells in the process (Chung et al. 2013, Noutel et al. 2011, Stephan et al. 2012). The improvement in tools to mark specific visual cell types and the experimental accessibility of the eyes has led to the rapid emergence of the mouse visual system for studies of nervous system development and plasticity. Here we consider the various steps leading to visual circuit development, with an emphasis on the emergence of the features we describe above in the section titled Functionally Distinct Processing Streams and Circuitries.

CONNECTING THE EYE TO THE BRAIN

Exiting the Eye and Growth to the Chiasm

The first major wiring process for long-range visual circuit development is to connect the eyes with the brain and, in that context, for RGC axons to grow toward the optic disc and nerve. This occurs during embryogenesis and is driven by repellant chemical cues in the retinal periphery such as chondroitin sulfate proteoglycans (Snow et al. 1991, Stuermer & Bastmeyer 2000) and by attractive cues expressed at the optic nerve head such as Netrin-1, acting through deleted in colorectal cancer (DCC) receptors expressed by RGC growth cones (Deiner et al. 1997). RGC axons then grow down the optic nerve until they reach the optic chiasm at the base of the brain. There, RGC axons destined for ipsilateral visual nuclei turn laterally, away from the midline, whereas contralateral-intended axons cross through the midline to the opposite brain hemisphere (Petros et al. 2008).

Laterality at the Optic Chiasm

The binary routing of RGC axons at the optic chiasm is governed in large part by the transcription factor Zic2, which is expressed in RGCs that turn ipsilaterally (Bhansali et al. 2014, Herrera et al. 2003, Petros et al. 2008, Rebsam et al. 2012, Sánchez-Arrones et al. 2013). Zic2 drives expression of the kinase receptor EphB1, which in turn responds to repellant ephrin-B2 expressed at the chiasm (Petros et al. 2010). In the mouse, Zic2 is expressed by a restricted set of RGCs in the ventrotemporal retina and, interestingly, by a small subset of RGCs in the far nasal retina that also stay ipsilateral (Herrera et al. 2003). The axons of RGCs whose somas reside outside the ventrotemporal retina, as well as those of late-born RGCs residing in the ventrotemporal retina, ignore the repellant ephrin-B2 to cross at the chiasm to project to the contralateral brain (Petros et al. 2008). Their crossing is not merely a passive behavior; these contralateral-projecting RGCs are identified by the expression of Islet2 (Pak et al. 2004) and SoxC (Kuwajima et al. 2017) and respond directly to factors such as neuronal cell adhesion molecule (NrCAM) and Plexin-A1 that facilitate the crossing of contralateral axons directly by causing a reversal in the growth-suppressing effects of Semaphorin6D (Kuwajima et al. 2012). One open question is whether the same RGC types are included in both ipsilateral- and contralateral-projecting populations or whether there are biases in the proportion of cell types that contribute to each projection pattern. Indeed, understanding how different RGC types develop their unique patterns of pathfinding and wiring is one of the major unmet goals of the field.

Selecting a Retinorecipient Target

Beyond the optic chiasm, there are >40 distinct image-forming and non-image-forming RGC targets in the brain (Morin & Studholme 2014). As a field, we are just starting to elucidate the full range of different RGC classes and their targets and have only a rudimentary understanding of the mechanisms that direct specific RGCs to different brain areas. An important and fundamental question is, how do different RGCs know which brain areas to target? For example, in the image-forming system, how do RGC axons know whether to target the dLGN, SC, or both?

Cellular Mechanisms of Axon-Target Matching

At the cellular level, RGC axon-target matching involves both directed targeting and a process of refinement that is intimately related to the timing of RGC neurogenesis. Genetic marking of different RGC types combined with birthdating markers allowed Osterhout et al. (2014) to discover that early-born RGCs innervate multiple incorrect brain targets, while most of the excess branches are subsequently removed. Later-arriving RGC projections chose their targets much more accurately and avoid a significant pruning stage. Moreover, different RGC types are born at different stages, leading to the formation of unique circuitries one after the other. It is still unclear whether this reflects the progressive restriction of target neuron availability or a specific strategy designed to more closely pair RGCs and their targets. This question should be resolved through deletion experiments in which one of the early-born RGC types is eliminated, or experiments in which RGC identity is altered. Tampering with the transcriptional machinery that governs RGC-type identity allows this sort of experiment to be done.

Another open question is whether laminar-specific targeting of RGCs—a feature that is salient in the dLGN and SC (**Figures 2** and **9**)—is governed by a similar mechanism as overall axon-target matching. Some RGC types, such as the Off-alpha RGCs, undergo a process of refinement to target the deeper portion of the SGS (Cheng et al. 2010, Huberman et al. 2008a). Since virtually every specific subset of RGC types targets a particular layer of the dLGN and SC (Hong et al. 2011; Kay et al. 2011; Kim et al. 2008, 2010; reviewed in Dhande & Huberman 2014a, Dhande et al. 2015b), and this layer-specific targeting preserves and relays specific receptive field properties from the retina to higher-order visual centers (Cruz-Martín et al. 2014), understanding the relative order and dynamics of this layers-specific wiring is crucial. Work from Sanes and colleagues (Hong et al. 2011, Kim et al. 2010) showed that, like overall target choice, there is variation in the degree of specificity with which different RGC types target the correct layers in the SC and dLGN. Moreover, retinal axon ingrowth regulates the timing of cortical axon innervation of the dLGN, in part through the transient expression of a repellent molecule that prevents premature entry (Brooks et al. 2013, Seabrook et al. 2013a). Corticogeniculate axons in turn regulate the innervation of the dLGN by retinal axons (Shanks et al. 2016).

Molecular Mechanisms of Axon-Target Matching

What molecular factors regulate RGC axon-target matching? Recent work shows that cellular adhesion plays a key role, at least in the non-image-forming system (Osterhout et al. 2011) (**Figure 11**). A subset of intrinsically photosensitive and related non-image-forming RGCs express Cadherin-6 (Cdh6), a Type II classical cadherin (Takeichi 1990). Their targets in the brain also selectively express Cdh6, and genetic removal of Cdh6 causes a severe reduction in the number of these RGCs that target their respective brain areas (Osterhout et al. 2011); instead, the

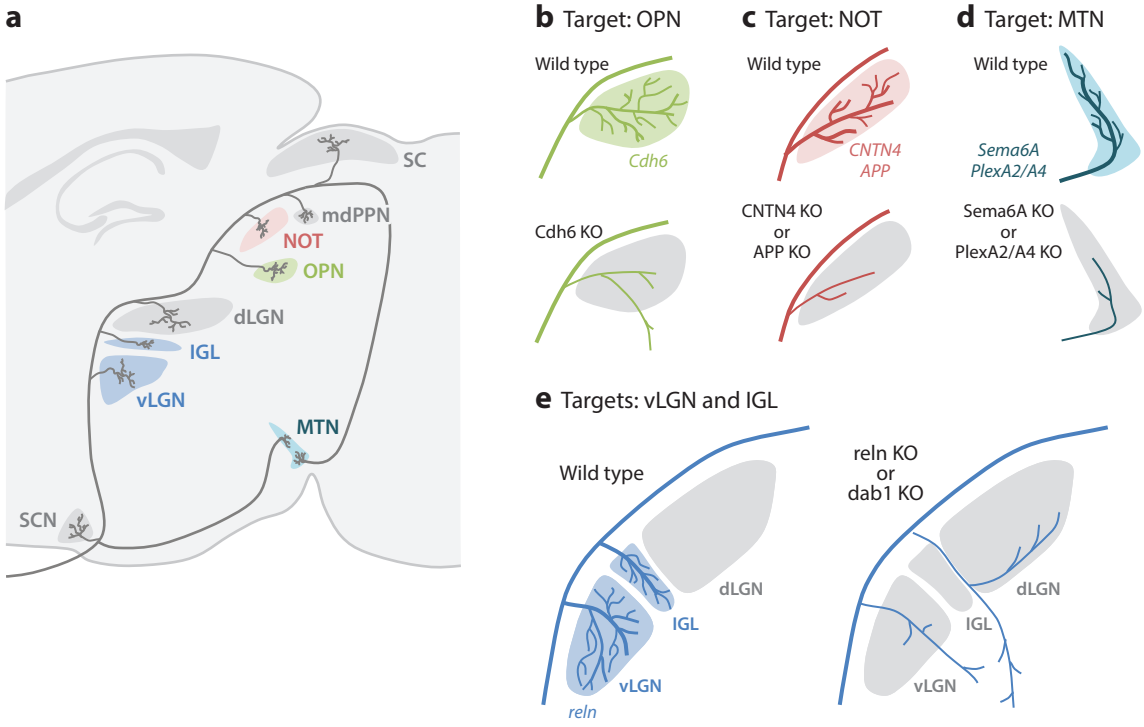


Figure 11

Molecular mechanisms regulating axon-target matching in the mouse visual system. (*a*) Subcortical visual pathway. (*b*) Cdh6 mediates targeting of RGCs to the OPN. (*c*) RGC innervation of the NOT is facilitated via interactions between CNTN4 and APP. (*d*) Sema6A and PlexA2 and A4 control RGC axon-target matching in the MTN. (*e*) Reln ensures correct targeting of RGC axons going to the vLGN and IGL. Abbreviations: APP, amyloid precursor protein; Cdh6, Cadherin-6; CNTN4, Contactin-4; dab1, disabled-1; dLGN, dorsal lateral geniculate nucleus; IGL, intergeniculate nucleus; KO, knockout; mdPPN, medial pedunculopontine nucleus; MTN, medial terminal nucleus; NOT, nucleus of the optic tract; OPN, olivary pretectal nucleus; reln, reelin; SC, superior colliculus; SCN, suprachiasmatic nucleus; Sema6A, Semaphorin-6A; PlexA2/A4, Plexin-A2/A4; vLGN, ventral lateral geniculate nucleus.

neurons overshoot to the more distal SC. In the accessory optic system (AOS), On DSGCs and a subset of On-Off DSGCs project to nuclei in the dorsal and ventral brainstem (Dhande & Huberman 2014a; Dhande et al. 2013, 2015b; Yonehara et al. 2009). A screen of expression patterns of IgG superfamily proteins and analysis of the genetically tagged RGCs reveal that they express Contactin-4 (CNTN4), and biochemical experiments confirm they also express amyloid precursor protein (APP), the loss of either of which leads to defects in DSGC-to-AOS wiring and associated behavioral defects in image stabilization (Osterhout et al. 2015). Remarkably, ectopic expression of CNTN4 in individual RGC types that normally avoid the AOS induced them to form and stabilize inputs to AOS nuclei, revealing a causal instructive role for CNTN4 in this process and suggesting that, more generally, individual molecules and their coreceptors (in this case, APP) and ligands tightly regulate axon-target matching (Osterhout et al. 2015). Kolodkin and coworkers (Sun et al. 2015) also beautifully showed that Plexin-Semaphorin interactions are crucial for connecting On-type RGCs to the ventral brainstem targets that ensure vertical image stabilization in the AOS.

To date, specific guidance or adhesion cues for regulating laminar targeting of the dLGN or SC in a lock-and-key manner (or by repulsion, for that matter) have not been identified, but resolving

how laminar targeting emerges is of critical importance and will also likely inform how dLGN neurons wire to specific layers of V1. Still, important work has shown that molecular systems such as reelin and its receptors, VLDLR and LRP8, together serve to link specific RGC types to their correct target regions of the dLGN by controlling target cell position and migratory patterns (Su et al. 2011, 2013).

RETINOTOPIC MAP DEVELOPMENT

Once axons find their correct targets and layer within that target, they have to map to the correct retinotopic location. There is robust evidence for an essential role of the EphA/ephrin-A receptor/ligand gradient system in mapping the azimuth axis of the eye onto the brain (dLGN and SC) (Triplett & Feldheim 2012). Perhaps the most compelling data stem from the disrupted topography that manifests as mistargeted retinotopic projections in mice that lack all three of the ephrin-A ligands normally expressed in the mammalian SC (Cang et al. 2008, Pfeiffenberger et al. 2006). The EphB/ephrin-B system may play a similar role for mapping the elevation axis of the eye in central targets (McLaughlin et al. 2003, Triplett & Feldheim 2012), but the experimental evidence for this is not as consistent. For one, the mapping phenotypes of EphB/ephrin-B mutant mice are less apparent than the EphA/ephrin-A mutants, and the mechanism (biased medial or lateral branching at the target) is not as obviously suited to topographic mapping. Second, other gradient systems may act in concert with (or instead of) EphB/ephrin-B, including Wnt/Ryk signaling (Schmitt et al. 2006). Additionally, pretarget dorsal/ventral sorting of RGC axons in the ascending optic tract (before reaching the dLGN or SC) may preferentially bias axons to the correct position before entering each target (Chan & Guillery 1994, Plas et al. 2005), reducing the requirement for a target-level gradient matching system for mapping the elevation axis. This pretarget sorting mechanism may similarly act through EphB/ephrin-B, other molecular factors, or both (Plas et al. 2008), with a variety of cell adhesion molecules such as L1 neural cell adhesion molecule (Dai et al. 2012), activated leukocyte cell adhesion molecule (Buhusi et al. 2009), NrCAM (Dai et al. 2013), or even EphA/ephrin-A (Suetterlin & Drescher 2014).

Neural Activity in Retinotopic Map Development

Early experiments established that neural activity contributes to retinotopic map development (Cline & Constantine-Paton 1989, O'Leary et al. 1986). Given that subcortical topographic mapping occurs when mouse eyelids are still closed (and retinal photoreceptors are not functionally integrated in the retina), this activity is not due to visual sensory experience and appears instead to be generated spontaneously (Galli & Maffei 1988, Meister et al. 1991). Shatz and colleagues demonstrated that this activity comes in the form of acetylcholine receptor–mediated correlated retinal waves (Feller et al. 1996, Meister et al. 1991) that propagate in vivo up the visual neuraxis to the dLGN, SC, and visual cortex (Ackman et al. 2012). Although interfering with either the amount or spatiotemporal pattern of this activity disrupts cell-intrinsic topographic map formation in the dLGN and SC (Burbridge et al. 2014, Grubb & Thompson 2003, McLaughlin et al. 2003, Pfeiffenberger et al. 2006, Xu et al. 2011, Zhang et al. 2012), RGCs (in the same retina) that experience normal retinal waves retain normal topographic and eye-specific projections (Burbridge et al. 2014). This links topographic map refinement directly to correlated RGC activity from spontaneous retinal waves and supports the view that map development is instructed through a combination of early chemotropic factors and patterned spontaneous activity.

Surprisingly, retinotopic targeting (topography) of ipsilateral RGCs appears to be regulated, at least in part, through distinct mechanisms, specifically by members of the teneurin family

of homophilic transmembrane glycoproteins (Leamey & Sawatari 2014). In particular, Ten-m3 and Ten-m2 mutant mice have mapping defects that are restricted to RGCs that project to the ipsilateral hemisphere (Dharmaratne et al. 2012, Leamey et al. 2007, Young et al. 2013). This suggests that there are unique retinotopic mapping mechanisms for ipsilateral- and contralateral-projecting RGC axons whose cell bodies are intermingled within the retinal binocular zone.

Mapping Space to and Within Visual Cortex

The mapping of dLGN axon projections to the visual cortex is likely governed by molecular and activity-dependent factors similar to those responsible for mapping retinogeniculate projections, including EphA/ephrin-A gradient matching (Zhao et al. 2013) and retinal waves (Ackman et al. 2012). Chronotopy is also thought to contribute to targeting and mapping dLGN projections to V1, perhaps through a coordinated interaction with reciprocally projecting corticothalamic neurons—the so-called handshake hypothesis (Molnár & Blakemore 1995). Although retinotopic receptive fields in V1 are disordered in mice that lack normal retinal waves (Cang et al. 2005, 2008), the specific role of geniculocortical activity in this mapping process remains uncertain, as activity manipulations to date have not specifically disrupted geniculocortical activity while leaving retinal and corticocortical activity intact. The retinotopic structure of higher-order visual areas is presumably relayed functionally from V1 via long-range connections and specific patterns of connectivity (Garrett et al. 2014, Marshel et al. 2011, Wang & Burkhalter 2007). However, relatively little is known about mechanisms governing development of these intracortical connections or the developmental features of the numerous rodent extrastriate visual cortical areas.

The dLGN and SC receive direct input from the retina and retinotopically aligned feedback projections from the visual cortex (layer 6 cells for dLGN, layer 5 cells for SC). That is, a given local region of the dLGN or SC receives feedforward (from the retina) and feedback (from the visual cortex) input from matched retinotopic locations. The development of these matched projections reflects the economical use of the same receptor-ligand matching systems and is assisted by activity-dependent refinement (Phillips et al. 2011, Triplett et al. 2009, Wang et al. 2015, Zhao et al. 2013).

DEVELOPMENT OF BINOCULAR MAPS

The mechanisms responsible for the development and plasticity of eye-specific projections in the dLGN, SC, and V1 have been a subject of intensive research since these segregated projections were first described in cat and primate (Hubel & Wiesel 1969, Rakic 1976). Their initial formation does not require vision and, similar to retinotopic map refinement, occurs before true visual experience is possible (Crair et al. 2001, Horton & Hocking 1996, Rakic 1976, White et al. 2001). A reasonable extrapolation from these results is that the targeting and segregation of these eye-specific projections is dictated by a molecular force or process, perhaps the same or a related one that is responsible for guiding crossing at the optic chiasm. However, unlike the success achieved in identifying molecular mechanisms governing chiasm crossing (Petros et al. 2008), target selection (Osterhout et al. 2011, 2015; Sun et al. 2015), and retinotopic map development (Cang & Feldheim 2013, Triplett 2014), molecular factors that directly govern eye-specific segregation (and not retinotopy) have not been identified. A diverse array of retinal activity manipulations, however, are known to interfere with the process of eye segregation (Huberman et al. 2008a). Similar to their role in topographic map development, retinal waves are believed to aid concurrently in the segregation of eye-specific projections. This spontaneous activity-mediated circuit refinement is thought to rely, at least in part, on a mechanism that translates correlations in RGC activity to pattern and

refine circuits (Butts et al. 2007). For example, changing the timing of the activity in the two eyes (making the largely random spontaneous activity more synchronous) disrupts eye segregation (Zhang et al. 2012), as does breaking retinal waves into smaller, local domains (Xu et al. 2011). Increasing wave synchrony or decreasing wave size does not, however, interfere with the emergence of retinotopic projections. Because local correlations are preserved with these manipulations, researchers believe this allows for activity-dependent refinement of topographic projections but disrupts eye-specific segregation through disruption of more global inter-eye activity comparisons. Eliminating activity completely, disrupting the correspondence between presynaptic (RGC) and postsynaptic (SC neuron) activity, or changing the local activity correlations also disrupts this refinement process, arguing for the contribution of a use-dependent competitive process that resembles Hebb's postulate (Bi & Poo 2001, Hebb 1949) and the "fire-together, wire-together" model (Burbridge et al. 2014, Shatz 1992).

Retinotopic and eye-specific mapping emerge at roughly the same time in the mouse. Xu et al. (2011) showed that a specific activity manipulation (inducing smaller retinal waves) disrupts eye segregation and retinotopy, but only in the binocular parts of the dLGN and SC. RGCs from the dorsal retina that encode and deliver visual information from a part of the world that is served by only one eye have normal retinotopic projections (their axon arbors are not expanded). Remarkably, enucleating one eye, which of course eliminates binocular interactions, rescues retinotopy for all remaining RGCs, even those relaying information from what would have been binocular regions of the retina. Similarly, artificially synchronizing activity in the two eyes through optogenetic manipulation disrupts eye segregation and retinotopy, although stimulating one eye at a time (asynchronously) has no effect on either (Zhang et al. 2012). Thus, retinotopic refinement of binocular RGC axons (from the ventrotemporal crescent of the retina) cannot proceed normally in the face of an activity manipulation that disrupts eye-specific segregation.

RECEPTIVE FIELD ALIGNMENT

Mice reared in the dark have clear binocular overlap of their On-Off receptive field subregions (subregion correspondence), although it is degraded in quality relative to mice reared normally (Sarnaik et al. 2014). Monocular On-Off subregion correspondence is unaffected by dark rearing, suggesting this aspect is not dependent on visual experience. B.-S. Wang et al. (2010) also showed that binocular correspondence of orientation preference gets better with visual experience but is still much more similar than chance early on, indicating that the initial molecular process of wiring that underlies receptive field organization is biased toward generating the correct patterns. Further improvement of matching (beyond what is there early on) requires visual experience, but again it exists without visual experience, which suggests intrinsic mechanisms that drive binocular matching.

Neurons in visual cortex have elongated receptive fields that respond best to specifically oriented lines such as bars and edges and are classified into two groups, simple and complex cells, based on the complexity of their responses (Hubel & Wiesel 1962). Wang et al. (2013) showed that binocular matching of orientation preference in complex orientation-selective cells is disrupted in mice forced to have a precocious critical period (by overexpressing brain-derived neurotrophic factor). Binocular matching occurs first in simple cells, then later in complex cells. The timing of binocular matching of simple cells is not changed in mice with a precocious critical period. Interestingly, the binocular matching of complex cells can be rescued by environmental enrichment [which many argue should be considered normal environment, as typical rearing conditions of laboratory mice are deprived environments (Würbel 2001)]. Thus, visual experience improves matching of receptive field properties but is not necessary at some baseline level for the emergence

and matching of basic receptive field properties, including matching of orientation preference between the eyes and correspondence of On-Off subregions.

Ko et al. (2013) examined the emergence of orientation-specific circuitry in the visual cortex (using two-photon imaging). Neurons demonstrated orientation selectivity and spatial frequency selectivity at eye opening (P13–P15) similar to that observed two weeks later, although the responses were more variable. However, specificity of local cortical connections improved in the two weeks following eye opening (Ko et al. 2013). This improvement occurred, although to a lesser extent, even when animals were dark reared (Ko et al. 2014). Thus, vision does not appear to be necessary for the emergence of basic V1 response properties and even some of the more intricate visual circuit properties. Nonetheless, fully elaborated features of the circuits and responses emerge only with visual experience.

The development of direction selectivity in visual cortex of the mouse occurs quite early (Rochefort et al. 2011). Moreover, the emergence of direction-selective responses does not require visual experience, which is at odds with results in the ferret (White & Fitzpatrick 2007) but may be consistent with the cat (Crair et al. 1998). The timing of development for direction-selective responses in V1 parallels the emergence of direction selectivity in the retina and thus may be retinally driven. Several groups are now pursuing this idea by specifically ablating retinal direction selectivity and assessing the impact on V1 responses. The field eagerly awaits the results of such experiments, as they stand to shed light on how specific cell types and their wiring may reflect nature's best solution to building visual circuitries that can encode the full range of environmental stimuli.

CONCLUSIONS AND FUTURE DIRECTIONS

There is considerable excitement about the progress made in understanding mouse visual system structure, function, and development in the past decade. As a consequence, the debate as to whether the mouse is an adequate model for vision is waning; instead, the comparisons between mouse and primates are now based on real data, and some general themes, if not principles, are starting to emerge. Moreover, discoveries in the mouse, such as the fact that the koniocellular-like streams of the mouse retinogeniculocortical pathway carry a preponderance of direction-selective cells, have raised new hypotheses about the primate visual system, some of which have been tested and are generating new models for primate vision (e.g., Zeater et al. 2015). In other words, the mouse is now starting to inform studies in the primate as well. One thing is abundantly clear now: The mouse is positioned squarely as a key model in the field of vision science and is here to stay.

One of our motivations in writing this review was to stimulate exploration of understudied areas. Here we offer mention of a few that urgently need data:

1. Extrastriate function: Our understanding of extrastriate visual areas—their local networks and functional contributions to vision in this species—is still scant. What do these areas contribute to vision, and how do these contributions differ across areas? Also, because V1 is multimodal in the mouse, is V1 more akin to extrastriate cortex of primates?
2. Better behavioral tests: This area is rapidly growing, but to understand what roles the various stations and their interconnections are serving in visual processing requires deeper understanding of the natural role that vision plays for the wild mouse as well as how learned behaviors and plasticity engage these brain areas in the lab setting. Do mice view each other's postures? How do they determine predator from conspecifics at distances where olfactory and somatosensory information is ambiguous or not available?
3. What is the role of multisensory integration? To what extent does the visual system work in concert with other sensory modalities to control navigation?

4. In terms of development, what are some of the nongraded expressions of molecules that govern target selection and laminar choice? For instance, little is known about how different dLGN neurons select different cortical layers or cell types. And how are the intricate polysynaptic circuits such as direction-selective retina-dLGN or SC-cortical pathways wired up to ensure laminar specificity? Are the same cues employed at each station—which would seem economical but has not been explored experimentally?
5. How do the mutations that impact visual wiring in the mouse relate to human diseases that cause blindness, deficits in plasticity, or degeneration?

Although the mouse visual system has recently become an increasingly important model for mammalian sensory function and development and impressive progress has been made in understanding it, questions such as these represent the next set of challenges for keeping this model relevant and for building toward translational tools to understand human vision and to treat human disorders. We should all be encouraged by the speed and extent to which the vision community has embraced the mouse, as well as grateful for the cautionary notes put forth by those who were rightfully concerned that the mouse does not faithfully represent all there is to know about visual function or development (see Baker 2013). There are now an ample number of key problems still to tackle in the field of mouse visual development, structure, and function. Based on the rapid progress made thus far, we feel the time is ripe to tackle the next set of key issues, and we are optimistic about where the field is going.

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