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Development of the Retina and Optic Pathway

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Abstract

Our understanding of the development of the retina and visual pathways has seen enormous advances during the past twenty-five years. New imaging technologies, coupled with advances in molecular biology, have permitted a fuller appreciation of the histotypical events associated with proliferation, fate determination, migration, differentiation, pathway navigation, target innervation, synaptogenesis and cell death, and in many instances, in understanding the genetic, molecular, cellular and activity-dependent mechanisms underlying those developmental changes. The present review considers those advances associated with the lineal relationships between retinal nerve cells, the production of retinal nerve cell diversity, the migration, patterning and differentiation of different types of retinal nerve cells, the determinants of the decussation pattern at the optic chiasm, the formation of the retinotopic map, and the establishment of ocular domains within the thalamus.

Keywords

proliferation; fate determination; migration; differentiation; stratification; mosaic; coverage; axonal outgrowth; decussation; retinotopic map; binocular segregation

Introduction

In 1986, when *Vision Research* published its 25th Anniversary Issue, there was no chapter dedicated to “developmental visual anatomy”, being the summary descriptor provided by the editors for the present chapter. The closest coverage was provided within a chapter on visual development, focusing upon the acquisition of visual function, the consequences of early visual deprivation or restricted visual exposure, and on the associated plasticity within visual cortex (Teller & Movshon, 1986). It is interesting to re-visit that historical overview now, twenty-five years later, to appreciate the excitement within the field during those golden years of visual neurophysiology. Three pioneers in our understanding of the development of the visual system received the Nobel Prize in Physiology or Medicine during that era, in 1981, Roger Sperry, David Hubel and Torsten Wiesel, and the contributions of two of them feature prominently within that article. As acknowledged by the authors, “In 1960, the neurobiology of visual development was dominated by the work of Roger Sperry”. But rather than this being the prelude to a tribute, Sperry is taken to task for his preoccupation

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with the hard-wiring of the visual pathway, and his impact for the era under review was largely dismissed: 'Sperry's relentless emphasis on the independence of neural *development* from neural *function* in the developing animal was to have a short life after 1961" (p. 1486, original italics).

Since that anniversary issue in 1986, the past twenty-five years have witnessed unprecedented experimental as well as conceptual advances in our understanding of the development of the retina and sub-cortical visual pathways, much of it occurring well before the onset of visual function. Many of these advances vindicate a hard-wiring perspective such as Sperry's, relying upon cell-signaling interactions independent of neural transmission, while others show that neural function long before the onset of photo-transduction plays a critical role in the formation of neural circuitry. The phenomenal scientific pace of the past twenty-five years has been made possible largely by new technologies that continue to expand the front of developmental neurobiology in general. The experimental advances have been a consequence of the revolution in molecular biology and by the availability of new imaging technologies, permitting genetic dissection of the molecular factors and cellular interactions underlying retinal and optic pathway development, and the visualization of single neurons or populations of cells as they pass through the cell cycle, express transcription factors and the downstream genes they regulate, migrate to their specific layers, differentiate their characteristic morphologies, navigate an axonal trajectory to central visual structures, establish and refine their synaptic connections, and undergo programmed cell death. The present review will not consider in detail those technical advances themselves; the reader is directed to another recent colorful review providing ample coverage of "this ever-expanding toolbox" (Mason, 2009). The consequent experimental results have led to new conceptual insights, altering the ways in which we think about retinal development and target innervation, and the present focus will be upon these changes in our understanding.

One should not fault the myopia of the former review too much; without a doubt, we simply could not appreciate the full nature of the neurobiological issues at play twenty-five years ago[1]. Visual cortex was where the action was, and electrophysiology was the tool of choice for understanding the mechanics underlying visual function. We now know so much more about the pre-visual development of the retina and sub-cortical visual pathways, from a decidedly cellular and molecular biological perspective, that I will restrict the present coverage accordingly, and unashamedly, as *vision* will hardly be mentioned.

By comparison with the other chapters in this special issue of *Vision Research*, the purview of the present chapter is vast, encompassing advances not only in our understanding of the various components establishing the complex architecture and connectivity of the neural retina, but also of the visual pathways and their innervation of target visual structures. Any such review of strides taken over a defined period of time must to some extent be idiosyncratic (as in that former paper), but I believe these issues largely summarize the major conceptual and experimental advances during the past twenty-five years. I have chosen to highlight eight issues, briefly recapitulating these advances and sacrificing much detail due to space limitations. Each of these topics has been reviewed in far greater detail elsewhere, and doubtless researchers working on development of the visual system will find reason enough to feel frustrated by the brevity of the present effort. Rather, my intended audience has been that collection of vision researchers that digest the literature on retinal and pathway development with only modest fervor, to give them a synopsis of the major advances during this era, as well as current students and post-docs working within this field

[1]That said, it is interesting to note that roughly one-third of the twelve-hundred fifty citations to Sperry's 1963 "chemoaffinity" paper (as of 2010) occurred before 1986.

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of developmental neurobiology that may not appreciate the degree to which this field has advanced. The latter group need only compare the coverage of the developing retina and visual pathway provided by textbooks then in use (e.g. Jacobson, 1978; Purves & Lichtman, 1985) with that provided more recently (Sanes, Reh, & Harris, 2006) to appreciate the remarkable evolution in our understanding of these developmental processes. The former textbooks reflect the strong foundations of the field drawn from experimental embryology and neurophysiology but now seem sadly deficient in providing much account of the histotypical interactions between cells or of the genes expressed and molecular signals they set in motion that participate in these events.

Development of the retina

Twenty-five years ago, while we had some appreciation that an early eye field was derived from the neural plate and was critical for the development of the retina, we had no knowledge of the transcriptional control of this process by a handful of early eye-field genes that are now understood to command a downstream cascade of genes critical for assembling the mature retina (Zuber & Harris, 2006). As the eye cup emerges and expands in size, the factors modulating cell cycle kinetics have been dissected with increasing detail, including the molecular mechanisms driving interkinetic nuclear translocation, the intracellular and extracellular determinants of cell-cycle exit, and the factors that coordinate the wave of neurogenesis progressing from its site of initiation (Agathocleous & Harris, 2009; Baye & Link, 2007; Del Bene, Wehman, Link, & Baier, 2008; Dyer & Cepko, 2001; Levine & Green, 2004; Martins & Pearson, 2008; Norden, Young, Link, & Harris, 2009). The present coverage will begin with the emerging neural retina at the outset of neurogenesis, considering advances in our understanding of the lineage relationships between retinal neurons, the determination of neuronal cell-types and the production of species-specific retinal architecture, the control of neuronal positioning, and the determinants of morphological differentiation.

1. What are the lineal relationships between the different cell types of the retina?

Retinal progenitors were understood to expand the pool of post-mitotic precursor cells that would ultimately adopt various cellular fates, but there was no firm understanding of whether dedicated progenitors yielded particular types of cell, or if progenitors were multi-potent. While birth-dating studies had already shown that each type of retinal nerve cell was born in a distinct window during retinal neurogenesis (Carter-Dawson & LaVail, 1979; Dräger, 1985; Hinds & Hinds, 1979; Sidman, 1961; Young, 1985), these provided no insight into the clonal relationships between the cells of the retina. In the late 1980s, two different approaches were employed to label single retinal progenitor cells in order to identify their progeny at subsequent stages of maturity. One was to inject single cells with cytoplasmic tracers that would remain detectable within progeny despite progressive dilution following repeated cell divisions (Holt, Bertsch, Ellis, & Harris, 1988; Wetts & Fraser, 1988). The other was to use replication-deficient retroviruses encoding reporter genes to infect single cells, therein bypassing the problem of progressive dilution with repeated mitoses (Turner & Cepko, 1987; Turner, Snyder, & Cepko, 1990). Both approaches yielded comparable findings, that retinal progenitor cells were in fact multi-potent, producing clones of cells that included a variety of retinal neuronal types as well as Müller glia. They lacked, however, any retinal astrocytes, handily accounted for, at roughly the same time, by the demonstration that astrocytes are immigrants to the neural retina, being derived from a distinct progenitor cell in the optic stalk and migrating into the inner retina during the period of retinal neurogenesis (Ling & Stone, 1988; Stone & Dreher, 1987; Watanabe & Raff, 1988).

The retinal clones arising from such multi-potent progenitors were striking in their heterogeneity, particularly within the mouse retina, some containing relatively few cells

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while others containing in excess of 100 cells, averaging around 50 per clone (Turner et al., 1990). Not surprisingly, when progenitors were labeled at earlier stages during the neurogenetic period, clones were typically larger and included more cell types, specifically, those known to be generated at such earlier stages (Fekete, Perez-Miguelsanz, Ryder, & Cepko, 1994; Turner et al., 1990). Much of the variability at a given age had been interpreted to reflect the lineage-independence of fate assignments–that the micro-environment of the developing retina was largely responsible for ascribing a specific fate to a given precursor after it had left the cell cycle. This was challenged by other labeling strategies that marked retinal progenitors far earlier during development, suggesting a basic consistency to clonal organization in the mouse retina (Reese, Necessary, Tam, Faulkner-Jones, & Tan, 1999; Williams & Goldowitz, 1992a; 1992b). The retinas of such chimeric mice showed clones that maintained some approximation to a constant ratio of rods, bipolar cells, Muller glia and amacrine cells. The estimated number of such clonal units was far in excess of the number of cells making up the sparsest retinal cell types, consistent with some heterogeneity between retinal clones lacking certain minority cell types, but these results suggested some of the previously documented variability in clonal consistency in the rodent retina as being simply a consequence of tapping into the lineage tree at variable times and/or branches. More recently, other researchers have reported conspicuous variability in retinal clones when identified from the outset of neurogenesis, in *Xenopus* (Wong & Rapaport, 2009). Some of this discrepancy with the data from mouse may ultimately prove to be explained by a relative constancy in the clonal amplification of later-generated and predominant cell types typical of nocturnal rodents. Still others have found a surprising degree of reproducibility in the clonal constituency arising from progenitors expressing the transcription factor *Ath5* (Poggi, Vitorino, Masai, & Harris, 2005), suggesting a strongly cell-intrinsic constraint on cellular fate.

The fact that birth-dating studies described, for nearly all species examined, gradients of neurogenesis for each type of cell that showed substantial spatio-temporal overlap (Harman & Beazley, 1987; Harman, Sanderson, & Beazley, 1992; Rapaport, Fletcher, LaVail, & Rakic, 1992; Rapaport, Wong, Wood, Yasumura, & LaVail, 2004; Reese & Colello, 1992; Sidman, 1961; Walsh & Polley, 1985; Young, 1985) was regarded as further evidence of a multi-potentiality amongst retinal progenitor cells that was not lineage-restricted. Nevertheless, certain trends were becoming increasingly apparent across species, in particular, that there was a conserved temporal ordering to these neurogenetic windows for the different cell types. Retinal ganglion cells were the first cell type to be produced, followed by horizontal cells and cones, while amacrine cells, rods, bipolar cells and Muller glia were produced progressively later (see Rapaport, 2006, for review). Given the temporal overlap in the neurogenetic windows for individual cell types in a patch of retina, it remained unclear whether single progenitors yielded cell types in a strict order, or if local variations in microenvironmental signals that changed over time were solely responsible for determining the fates of neighboring cells born at the same time.

This issue was only very recently resolved in *Xenopus*, by identifying the constituents of single labeled clones marked at the earliest stages of eye-cup formation that had also been exposed to bromodeoxyuridine (Brdu) at some variable stage for the remainder of neurogenesis. The lack of Brdu, therefore, was a reliable indicator that a given cell in the clone had been born prior to all of the other Brdu+ cells within the clone. What was critically observed in this study was that there was a directionality in the order of cell production: once production of a particular cell type had commenced within a clone, the subsequently generated progeny within that clone virtually never included any members of those types that had already commenced neurogenesis earlier (Wong & Rapaport, 2009). Retinal progenitors, it would appear, are multi-potent, but their multi-potentiality declines as development proceeds. Not every progenitor will yield every type of retinal cell, but for

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those cell types that it does yield, they are produced in a precise ordering (figure 1). Unidirectional changes in competence apparently occur cell-autonomously, accounting for the fact that a progenitor might very well yield a cell type for which its immediate neighbor is no longer competent for production.

2. How is the diversity of retinal cell types established?

This cell-autonomous behavior is only presumed to restrict the potentiality of retinal progenitors, not to specify the precise constituents that are produced within any particular clone. Twenty-five years ago, the role of environmental signals that impinge upon dividing progenitor cells and post-mitotic precursors was being investigated primarily using dissociated cell and retinal explant culture assays, but there was relatively little appreciation for the role of cell-intrinsic determinants that are now understood to participate in this process, permitting, repressing or directing cell fate decisions (but see Reh, 1991). The role of environmental signals, including those produced by newly differentiating cells of a given type that inhibit production of the same cell type, have been amply reviewed (Adler, 2000; Agathocleous & Harris, 2006; Lamba, Nelson, Karl, & Reh, 2008; Levine, Fuhrmann, & Reh, 2000; Lillien, 1998; Reichenbach et al., 1998). Some of those earlier studies described the fate changes produced *in vitro* when cultured cells developed in the presence of a particular type of cell (Waid & McLoon, 1998; Watanabe & Raff, 1990; 1992), while a few others sought to ablate a hypothesized cellular source of a signaling molecule *in vivo* and examine changes in the production of subsequently generated neurons (Reh & Tully, 1986; Tyler, Carney, & Cameron, 2005). More refined *in vivo* manipulations of gene expression in single labeled progenitors have subsequently shown how clonal constituency can be altered dramatically by upregulating ligand or receptor expression (e.g. Dorsky, Chang, Rapaport, & Harris, 1997; Lillien, 1995). For instance, Notch-Delta signaling between retinal progenitors has been shown to regulate proneural gene expression (see Ohsawa & Kageyama, 2008, for review). Such lateral inhibitory interactions between an initially equi-potential population ensure that not all progenitors start producing post-mitotic precursors at the same time (vertical grey arrows in figure 1). As a minority come to experience less Notch receptor activation, activating their own proneural genes leading to the commitment and differentiation of early-generated cell types (e.g. a retinal ganglion cell), so these early-generated neurons produce signals within the local environment that influence cell fate choice. It is a simple matter to envision progressively later-generated cell types, as they get added to this evolving microenvironment and begin to differentiate, creating additional signals that further impinge upon progenitors and precursors, signaling or constraining fate assignments or providing differentiation signals (colored arrows in figure 1). Curiously, manipulations that eliminate a type of retinal neuron show greatest effects upon the subsequent production of like-type cells, and relatively little impact upon other later-generated cells (Mu, Fu, Sun, Liang, Maeda, Frishman & Klien, 2005; Reh & Tully, 1986; Tyler et al., 2005; Waid & McLoon, 1998; Williams, Cusato, Raven, & Reese, 2001).

Not all progenitor cells or newly post-mitotic neurons in the local micro-environment may be competent to respond to these signals, however, and it is this field of developmental neuroscience that has witnessed explosive growth in the past two decades due to the revolution in molecular biology yielding fresh insight into the control of neuronal fate and differentiation, and how such mechanisms relate to the control upon proliferation (Agathocleous & Harris, 2009; Livesey & Cepko, 2001; Trimarchi, Stadler, & Cepko, 2008). For instance, the role played by individual transcription factor genes can now be assessed by determining whether proliferating cells or postmitotic precursors express them (Jusuf & Harris, 2009; Poggi et al., 2005), and by examining the retinal phenotype or the cellular morphogenesis when such genes (singly or in combination) are knocked out or overexpressed (Akagi, Inoue, Miyoshi, Bessho, Takahashi, Lee, Guillemot & Kageyama,

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2004; Badea, Cahill, Ecker, Hattar, & Nathans, 2009; Feng, Xie, Joshi, Yang, Shibasaki, Chow & Gan, 2006; Oh , Khan, Novelli, Khanna, Strettoi & Swaroop, 2007); by examining the clonal phenotype arising from infected or electroporated progenitor cells in which gene function is altered (Dyer, Livesey, Cepko, & Oliver, 2003; Matsuda & Cepko, 2007); by defining the downstream genetic consequences following gene deletion (Mu & Klein, 2008; Yoshida, Mears, Friedman, Carter, He, Oh, Jing, Farjo, Fleury, Barlow, Hero & Swaroop , 2004); by identifying the gene expression profile of single cells (Cherry, Trimarchi, Stadler, & Cepko, 2009; Trimarchi, Stadler, Roska, Billings, Sun, Bartch & Cepko, 2007; Trimarchi et al., 2008); and by defining the upstream regulatory mechanisms controlling gene expression itself (Cherry et al., 2009; Hsiau, Diaconu, Myers, Lee, Cepko & Corbo, 2007; Kim, Matsuda, & Cepko, 2008; Trimarchi et al., 2007; 2008; Willardsen, Suli, Pan, Marsh-Armstrong, Chien, El-Hodiri, Brown, Moore & Vetter, 2009).

A variety of transcription factors, mostly of the basic helix-loop-helix (bHLH) and homeodomain families, have been shown to be expressed by subsets of retinal progenitor cells or their post-mitotic progeny, the retinal precursor cells, at particular periods during retinal development, and to be critical for the acquisition of particular retinal fates or for their subsequent differentiation into particular types of a given cell (Ohsawa & Kageyama, 2008). Indeed, the simple inactivation or mis-expression of many of these genes can lead to striking alterations in the cellular composition of the retina, in some cases, specific for single types of cell, due to adoption of an alternative fate, or to a failure to differentiate correctly, often followed by cell death. For example, one of the earliest expressing of these genes is *Math5*, critical for the production of retinal ganglion cells, as when it is knocked out, the population of retinal ganglion cells is dramatically reduced (Brown, Patel, Brzezinski, & Glaser, 2001; Kay, Finger-Baier, Roeser, Staub, & Baier, 2001). As lineage-mapping studies (i.e. studies identifying the descendants of progenitors that had activated a particular gene) have shown that horizontal cells, amacrine cells and photoreceptors also descend from the population of progenitor cells that had expressed *Math5* during early development in the mouse retina (Yang, Ding, Pan, Deng, & Gan, 2003), this transcription factor was said to bestow competence to produce the ganglion cell fate rather than being a final fate-determining gene for ganglion cells (i.e. it is necessary, but not sufficient). *Math5* is subsequently downregulated in those cells fated to become retinal ganglion cells, when *Brn3b* and *Isl1* are then activated, each of which is critical for the differentiation of retinal ganglion cells (Mu, Fu, Sun, Beremand, Thomas & Klein, 2005; Pan, Deng, Xie, & Gan, 2008). *Math5* mutants show reduced *Brn3b* expression, and *Brn3b* knock-out mice show reductions in the size of the ganglion cell population (Gan, Wang, Huang, & Klein, 1999), as do *Isl1*-conditional knock-out mice (Elshatory, Everhart, Deng, Xie, Barlow & Gan, 2007). Different *Brn3* family members have recently been shown to participate in generating the diversity of retinal ganglion cell types (Badea et al., 2009), while *Isl1* also plays a role in the differentiation of other retinal cell types (see below). Exactly what controls ganglion cell fate specification downstream of *Math5* is unclear, although recent studies reinterpreting the role of *Brn3b* suggests it acts to specify ganglion cell fate rather than control differentiation (Qiu, Jiang, & Xiang, 2008).

Another transcription factor gene, *Foxn4*, plays a role in progenitor cells in the production of amacrine and horizontal cell fates, as its knock-out leads to a reduction in the former and a complete loss of the latter (Li , Mo, Yang, Price, Shen & Xiang 2004). Downstream of *Foxn4* lies *Ptf1a*, turning on only after terminal division (Jusuf & Harris, 2009), though showing a comparable phenotype when knocked out (Fujitani, Fujitani, Luo, Qiu, Burlison, Long, Kawaguchi, Edlund, MacDonald, Furukawa, Fujikado, Magnuson, Xiang & Wright, 2006). *Prox1*, in turn, is downstream of *Pt1fa*, being expressed in differentiating horizontal and amacrine cells, though is critical for acquisition of the horizontal fate alone (Dyer et al., 2003). Amacrine cell fates, by contrast, are determined when *Pt1fa* is co-expressed in

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precursors along with two other competence factors, *NeuroD* and *Math3*, acting through *Barhl2* to drive the differentiation of glycinergic amacrine cells (Mo, Li, Yang, & Xiang, 2004), *BhlhB5* for GABAergic subtypes (Feng et al., 2006), and *Isl1* for cholinergic amacrine cells (Elshatory et al., 2007).

Otx2 plays a role in directing cells toward a photoreceptor fate, as its knock-out leads to their loss (along with bipolar cells), while virally-mediated expression in progenitor cells promotes a photoreceptor fate (Nishida, Furukawa, Koike, Tano, Aizawa, Matsuo & Furukawa, 2003). *Otx2* acts through the cone-rod homeobox gene *Crx*, also critical for the differentiation of photoreceptors (Furukawa, Morrow, & Cepko, 1997). Downstream of *Crx*, the ligand-activated transcription factor *Ror*β acts as a switch, directing photoreceptors to become rods, as its knock-out leads to this population of photoreceptors differentiating as cones (Jia, Oh, Ng, Srinivas, Brooks, Swaroop & Forrest, 2009). The rod-directive actions of *Ror*β are mediated through the downstream activation of the transcription factor *Nrl*, since its knock-out also yields this population of photoreceptors to differentiate as cones (Mears, Kondo, Swain, Takada, Bush, Saunders, Sieving & Swaroop, 2001), while the forced expression of *Nrl* in the entire *Crx*-expressing population leads to an outer nuclear layer composed exclusively of rods (Oh, Khan, Novelli, Khanna, Strettoi & Swaroop, 2007). *Nrl* in turn acts through *Nr2e3* to produce rod photoreceptors, for knock-out of the latter also yields a cone-like phenotype in cells that would have otherwise been rods (Corbo & Cepko, 2005; Haider, Naggert, & Nishina, 2001). In all three of these knock-outs, containing surplus cones at the expense of the rod photoreceptors, the former differentiate as UV-cones evidenced by their opsin expression phenotype. The establishment of M-cones requires the expression and activation of the thyroid hormone-activated transcription factor *Trβ2*, requiring *NeuroD* upstream of it for its expression, as knocking out either yields a lack of M cones (Liu, Etter, Hayes, Jones, Nelson, Hartman, Hartman, Forrest & Reh, 2008; Ng, Hurley, Dierks, Srinivas, Saltó, Vennström, Reh & Forrest, 2001; Roberts, Srinivas, Forrest, Morreale de Escobar, & Reh, 2006).

Bipolar cell production requires the presence of the bHLH transcription factors *Mash1* and *Math3*, for in the absence of both (but not either one alone), they fail to form altogether, becoming Müller glia instead (Tomita, Moriyoshi, Nakanishi, Guillemot, & Kageyama, 2000). Bipolar cells are also dependent upon the transcription factor gene, *Chx10*, for in its absence, these cells fail to form (Burmeister, Novak, Liang, Basu, Ploder, Hawes, Vidgen, Hoover, Goldman, Kalnins, Roderick, Taylor, Hankin & McInnes, 1996). *Chx10* is normally expressed in all retinal progenitors early, ultimately being retained only in bipolar cells, and is believed to play a repressive role upon other proneural genes like *Ath5* leading to the production of other cell-types (Vitorino, Jusuf, Maurus, Kimura, Higashijima & Harris, 2009). Bipolar cells also require *Isl1* expression, for its conditional knock-out yields a drastically reduced bipolar cell population consequent to cell death during the first postnatal week (Elshatory et al., 2007). Twelve different bipolar cell sub-types are present in the mouse retina (Wässle, Puller, Müller, & Haverkamp, 2009), and transcription factors critical for the differentiation and/or survival of some of these have been identified, including *Vsx1* and *Irx5* for multiple OFF-cone bipolar cell subtypes (Cheng, Chow, Lebel, Sakuma, Cheung, Thanabalasingham, Zhang, Bruneau, Birch, Hui, McInnes & Cheng, 2005; Chow, Volgyi, Szilard, Ng, McKerlie, Bloomfield, Birch & McInnes, 2004), *Bhlhb5* for the type 2 OFF-cone bipolar cell (Feng, Xie, Joshi, Yang, Shibasaki, Chow & Gan, 2006), and *Bhlhb4* for rod bipolar cells (Bramblett, Pennesi, Wu, & Tsai, 2004).

Müller glial cell production arises from terminal divisions following the genesis of all neuronal cell types, yielding two daughters, one differentiating as a bipolar cell or rod photoreceptor stipulated by the relevant proneural genes then present. The other daughter cell however, is inhibited from cell cycle re-entry, despite heightened Notch activation, due

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to higher levels of the cell cycle inhibitor p27/Kip1 in these later progenitors, differentiating as Müller glia instead (Dorsky, Rapaport, & Harris, 1995; Ohnuma, Philpott, Wang, Holt, & Harris, 1999). Down-regulating Notch activity, like the knock-out of either *Hes1* or *Hes5* (being downstream effectors of Notch activation that suppress proneural gene activity), all yield reduced Müller glial production, while mis-expression of these promote glial features (Furukawa, Mukherjee, Bao, Morrow, & Cepko, 2000; Hojo et al., 2000; Nelson, Gumuscu, Hartman, & Reh, 2006). *Sox9*, expressed initially in all retinal progenitors but ultimately turned off in all but the last-generated Müller glial cells, also participates in Müller glial specification, since knocking out *Sox9* function reduces Müller glial cells (Poché, Furuta, Chaboissier, Schedl, & Behringer, 2008), while Notch activity itself regulates transcription of *Sox9* (Muto, Iida, Satoh, & Watanabe, 2009). Indeed, Notch signaling later during retinal development may more actively promote the Müller glial fate, as well as repress particular types of neuronal fates, rather than simply repressing proneural gene expression (Jadhav, Mason, & Cepko, 2006; Yaron, Farhy, Marquardt, Applebury, & Ashery-Padan, 2006; see Jadhav, Roesch, & Cepko, 2009, for review).

The above summary, while showing the critical roles of various genes in fate specification and differentiation (if ignoring much of the nuances of interpretation, the documented species differences and other contradictions present within the literature, as well as the detailed understanding of the regulatory actions shown for some of these factors and the full spectrum of their effects), is undoubtedly simplifying the complex nature of the downstream gene regulatory events and combinatorial coding that yields the richness of retinal cell diversity (Agathocleous & Harris, 2006; Mu & Klein, 2008; Trimarchi et al., 2008). Furthermore, how those genes influencing fate specification are regulated within an increasingly heterogeneous population of progenitor cells, either through cell-intrinsic changes associated with subsequent cell divisions, or by way of extrinsic signals within the evolving microenvironment, are relatively under-explored. In a few cases, the signaling molecules and their receptors through which they modulate retinal fates have been shown to engage the above transcription factors, for instance, GDF11 and FGF controlling the window of retinal cell competence for ganglion cell production by modulating *Math5* (Kim, Wu, Lander, Lyons, Matzuk & Calof, 2005; Willardsen et al., 2009). The extent to which the population of progenitors is heterogeneous at the very outset of neurogenesis is also debated, as is the understanding of how such variation later on is established, and whether it is due to a reproducible program or reflects a stochastic component in the establishment of cellular biases (Agathocleous & Harris, 2006). The role of symmetric versus asymmetric divisions as a function of developmental time and in response to extracellular signals also remains to be understood (Cayouette, Poggi, & Harris, 2006). Likewise, studies are only beginning to dissect the determinants of the temporal window of neurogenesis, clarifying the nature of the signaling events that triggers its onset and spread (Agathocleous, Iordanova, Willardsen, Xue, Vetter, Harris & Moore, 2009; Hufnagela, Lea, Riesenberga, & Brown, 2010) and those that ensure an eventual cessation of divisions (Ohnuma, Philpott, Wang, Holt & Harris, 1999). But by conceptualizing fate specification in light of the above cell-intrinsic and environmental determinants, we can readily envision variations upon these themes that should lead to the characteristic differences between retinal organization in different species.

Vertebrate retinas conform to a basic organizational plan. Species differences are due primarily to differences in the ratios of the various constituent cell types, these differences being most apparent when comparing related nocturnal versus diurnal species. How those variations might come about during development is easy to imagine by modulating gene expression or function underlying the above intrinsic and extrinsic factors that confer retinal cell fate or direct differentiation (Reichenbach & Robinson, 1995; Reichenbach et al., 1998). That nature might do this through allelic variants of the above genes is suggested by

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considering the variation in retinal cell number in different strains of mice. Multiple retinal cell classes exhibit conspicuous differences in cell number that are independent of variation in retinal area between different mouse strains, for example, retinal ganglion cells (Williams, Strom, Rice, & Goldowitz, 1996), horizontal cells (Williams, Strom, Zhou, & Yan, 1998) and dopaminergic amacrine cells (Whitney, Raven, Ciobanu, Williams, & Reese, 2009). The genetic dissection of such variation in traits has blossomed in recent years, made possible by multiple resources. The genomes of inbred strains have been sequenced, making possible the identification of single nucleotide polymorphisms that underlie such genetic variation. There are a wide variety of mouse strain resources that can aid in this approach, including recombinant inbred strains (Williams, Gu, Qi, & Lu, 2001) and chromosome substitution strains (Singer, Hill, Burrage, Olszens, Song, Justice, O'Brien, Conti, Witte, Lander & Nadeau, 2004). There is as well an expanding gene expression database for eye and retinal transcripts derived from these same mouse strains (Geisert, Lu, Freeman-Anderson, Templeton, Nassr, Wang, Gu, Jiao & Williams, 2009), which can aid in the identification of candidate genes residing at such genomic loci where quantitative traits have been mapped.

For example, by using recombinant inbred mouse strains derived from two inbred laboratory strains for which the genomes have each been sequenced, such natural variation in cell number, which shows as much as a two-fold difference for the population of horizontal cells and a nearly four-fold difference for dopaminergic amacrine cells, can be mapped to discrete loci within the mouse genome, where allelic variants responsible for some of this natural variation must be present (Reese, Raven, Whitney, Williams, Elshatory & Gan, 2008; Whitney, Raven, Ciobanu, Williams & Reese 2009; Williams, Strom, & Goldowitz, 1998). While one could envision that some of this natural variation might be caused by polymorphisms in genes that modulate cell proliferation or cell cycle kinetics, affecting multiple populations of retinal neurons, to date, the variations in the populations of distinct retinal cell types between different strains of mice are not correlated (Whitney, Raven, & Reese, 2007), and the quantitative trait loci identified for each of these traits differ, suggesting that they are each modulated (within these strains, at least) independently, by affecting genes that influence fate assignment or differentiation (Reese et al., 2008), by modulating genes controlling cell survival (Whitney et al., 2009), or by some combination of these.

Recently, however, it has been suggested that alterations in cell-cycle exit decisions (i.e. the onset and termination of the neurogenetic period within the developing retina) may be a simple yet sufficient means of yielding substantial inter-species differences in retinal organization. The retinas of nocturnal versus diurnal species of new world monkey differ in the relative sizes of their rod and their cone photoreceptor populations, respectively. As the neurogenetic window for cone photoreceptor production precedes that for the rods in all species examined, perhaps the species differences arise from simply delaying cell-cycle exit relative to the temporal variation in environmental and cell-intrinsic factors described in the preceding section that impact fate assignments. The greater size of the rod photoreceptor population in the nocturnal monkey, *Aotus azarae*, correlates with another later-generated (and functionally related) cell type, the rod bipolar cells, while the size of the cone photoreceptor population is absolutely smaller, as is another early-generated retinal cell type, the retinal ganglion cell population, when compared with the diurnal monkey, *Cebus apella*. Consistent with the hypothesis that these differences in four types of retinal cell reflect a delay in cell-cycle exit decisions, the nocturnal species was shown to exhibit a protracted neurogenetic period, a shorter cell cycle at comparable maturational ages, and variation in cell-cycle associated genes or proteins that are in line with a delayed neurogenetic window (Dyer, Martins, da Silva Filho, Muniz, Silveira, Cepko & Finlay, 2009). Forcing single progenitors to withdraw prematurely from the cell cycle validates the expectation that later-generated cell types within identified clones are reduced in frequency

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(Dorsky et al., 1997; Dyer et al., 2003), so it will be interesting to witness the application of conditional transgenic strategies in the developing mouse retina to modulate the period of cell cycle withdrawal upon retinal architecture and the underlying populations of retinal neurons.

3. How do newborn neuroblasts migrate to their laminar destinations?

Retinal progenitors undergo mitosis at the ventricular surface, and for those divisions yielding a daughter cell that withdraws from the cell cycle, many of those neuroblastic precursors must then migrate to their future laminar destinations. Unlike the developing neocortex, where newborn neuroblasts migrate conspicuous distances at progressively later stages and benefit from a radial glial scaffold that guides them through an expanding white matter forming beneath the cortical plate, neuroblast migration in the retina was considered a simpler feat, played out over a shorter distance amongst a mixed population of progenitor and precursor cells that themselves should provide some degree of radial support for their migration. Early studies on the migratory behavior of newborn neuroblasts were largely speculative, based on Golgi-staining and electron microscopy studies at progressively earlier stages, from which inferences were drawn about the transitional stages of different types of neuron (Hinds & Hinds, 1974; 1979; 1983; Morest, 1970). They suggested that rod and cone precursors maintain an attachment at the ventricular surface following their final mitotic division, subsequently extending a basally directed radial process through which the nucleus translocates to achieve an eventual somal positioning within the outer (or sometimes winding up within the inner) nuclear layer (Spira, Hudy, & Hannah, 1984). For the other cell types, however, the means by which they migrated were harder to interpret in the absence of distinctive markers that also labeled the entirety of the cell. Antibodies that labeled the plasma membrane of distinct cell types provided one means of better inferring the migratory behavior of different cell classes, as have fluorescent reporter genes driven by cell-specific promoters. Imaging the latter *in vivo* has shown in greater detail the progressive changes in morphology in conjunction with neuroblast movement. These studies have suggested two distinct modes by which inner retinal neurons arrive at their final laminar positions:

The earliest born cells, the retinal ganglion cells, extend a leading (basally-directed) process through which the nucleus subsequently translocates (McLoon & Barnes, 1989). This radial process gives rise to the developing axon of the ganglion cell, extending across the inner retinal surface even before the nucleus has arrived at the future ganglion cell stratum itself (figure 2a–c). Ganglion cell differentiation may proceed to such an extent that the axon has navigated a course into the optic nerve well before somal translocation has been completed, evidenced by the fact that bipolar-shaped neurons at intermediate locations in the retinal neuroepithelium could be labeled from the developing optic nerve (Dunlop, 1990; Snow & Robson, 1994). The behavior of the trailing end of the cell is less clear: some studies provide evidence for a remaining attachment at the ventricular surface until translocation is completed (McLoon & Barnes, 1989), while other more recent *in vivo* imaging studies suggest that the cell relinquishes its apical attachment before translocation is completed (Poggi et al., 2005).

Such nuclear translocation may be a common means for retinal neuroblasts to achieve their final positioning. Even the cone photoreceptor cells exhibit such nuclear translocation (figure 2b–d), despite their attachment to the future outer limiting membrane and their eventual somal positioning adjacent to it (Poggi et al., 2005; Rich, Zhan, & Blanks, 1997). For these cells, like the rods, they extend a basally directed process, but one that does not extend to the inner retinal surface, particularly at later developing stages (Johnson, Williams, Cusato, & Reese, 1999). Bipolar cells also undergo a similar nuclear translocation, at the latest stages of retinal development, when the thickness of the developing retina is greatest. For this cell type, both the leading and trailing processes attach to their respective retinal

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margins (the inner and outer limiting membranes) as the nucleus translocates to the future inner nuclear layer (figure 2c–e). Subsequently, the inner and outer processes detach as axonal terminations form in the inner plexiform layer and after dendritic processes begin to emerge within the outer plexiform layer, respectively (Morgan, Dhingra, Vardi, & Wong, 2006).

Amacrine cells, by contrast, show a striking difference in their migratory behavior, undergoing active cellular migration without obvious leading or trailing processes directed to, or attached at, the inner retinal surface or ventricular surface, respectively (figure 2a–c). These cells had been described in Golgi preparations as having far more complex morphologies than the simpler bipolar shape associated with cells undergoing nuclear translocation (Prada, Puelles, Genis-Gálvez, & Ramirez, 1987), and more recent *in vivo* imaging studies have shown these cells to extend undirected processes that may participate in sensing the local environment during migration (Godinho, Mumm, Williams, Schroeter, Koerber, Park, Leach & Wong, 2005). Still other amacrine cells apparently retain a simple bipolar morphology as they migrate, though lacking attachments at either surface of the retina, but how this difference might relate to ultimate bipolar cell subtype is unclear (Prada et al., 1987). This behavior is more reminiscent of that for migrating horizontal cells, which adopt a generally bipolar morphology (figure 2a–b) lacking inner or outer attachments as they migrate away from the ventricular surface (Huckfeldt, Schubert, Morgan, Godinho, Di Cristo, Huang & Wong, 2009; Schnitzer & Rusoff, 1984).

The horizontal cells have attracted recent attention because they exhibit a unique aspect to their migratory behavior, overshooting the horizontal cell stratum (figure 2b) to coalesce within the future amacrine cell layer before migrating back to their final destination (Edqvist & Hallböök, 2004; Edqvist, Lek, Boije, Lindbäck, & Hallböök, 2008). Two further features of this process are worth nothing here: First, the apically directed migration, at least in the mouse retina, requires the transcription factor gene *Lim1*, for when it is conditionally knocked out, horizontal cells remain positioned at deeper locations within the inner nuclear layer amongst the amacrine cells, differentiating dendritic arbors within the inner plexiform layer (Poché, Kwan, Raven, Furuta, Reese & Behringer, 2007). Second, in the chick retina, the horizontal cells apparently re-enter the cell cycle and divide within these deeper locations before migrating apically, back to the horizontal cell layer (Boije, Edqvist, & Hallböök, 2009), consistent with other recent lineage-mapping studies suggesting that some progenitors divide to yield two horizontal cells of the same subtype (Rompani & Cepko, 2008). In the zebrafish, such divisions producing pairs of horizontal cells have been imaged *in vivo* to take place in the horizontal cell layer itself (Godinho, Williams, Claassen, Provost, Leach, Kamermans & Wong, 2007), after these cells have migrated back from the inner retina (Jusuf & Harris, 2009). This unique propensity to re-enter the cell cycle after migration and expression of horizontal cell-specific genes has been related to other recent demonstrations that mature horizontal cells can re-enter the cell cycle and give rise to retinoblastoma (Ajioka, Martins, Bayazitov, Donovan, Johnson, Frase, Cicero, Boyd, Zakharenko & Dyer, 2007).

4. How is cellular positioning upon the retinal surface determined?

Retinal nerve cell classes are distributed as regular retinal arrays, commonly referred to as retinal mosaics (Wässle & Riemann, 1978), and the patterning of such arrays was generally assumed to reflect a periodicity in the fate-determining events responsible for producing those nerve cell classes (e.g. McCabe, Gunther, & Reh, 1999), as is the case for the patterned distribution of photoreceptor types in the eye of *Drosophila* (Ready, Hanson, & Benzer, 1976). While such periodic fate determination events (outlined above) undoubtedly contribute to the grain of such mosaics (figure 3a), we now know from experimental studies that the final patterning of a mosaic is refined by cell death (figure 3b) and by cellular

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movements in the plane of the retina (figure 3c), at least for certain types of retinal nerve cell. Similar conclusions have been drawn from modeling studies seeking to simulate the role of fate determination events, cell death and tangential dispersion, either singly or in combination (Eglen & Willshaw, 2002; Eglen, 2006).

Interfering with naturally occurring cell death, for instance, yields mosaics of cholinergic amacrine cells and dopaminergic amacrine cells in which the minimal intercellular spacing between homotypic neighbors is reduced (as expected, given the increase in cell density). In addition, however, the resultant regularity of the mosaic is also degraded, suggesting that cell death serves to eliminate the closest near neighbors, thereby enhancing patterning (Raven, Eglen, Ohab, & Reese, 2003; Resta, Novelli, Di Virgilio, & Galli-Resta, 2005). Where the mosaics can also be identified reliably prior to naturally occurring cell death, they have been shown to be less ordered relative to later stages following cell death (Galli-Resta & Novelli, 2000). Yet in other mosaics that do not appear to be modulated by naturally occurring cell death (e.g. the horizontal cells), mosaic order increases at later developmental stages when cell number remains stable (Raven, Stagg, Nassar, & Reese, 2005b). Such experiments suggest that nerve cells move in the plane of the retina to space themselves apart, and are supported by other studies employing clonal boundary analysis, revealing such progressive tangential dispersion of particular types of retinal nerve cells (Reese, Harvey, & Tan, 1995; Reese et al., 1999). Very recently, live imaging of labeled horizontal cells has shown such tangential movements, providing the most direct evidence that these movements contribute to the improvement in mosaic patterning (Huckfeldt et al., 2009). Those studies implicate early differentiating dendritic interactions in defining a domain within which the soma of a cell will occupy a central location; subsequent events may then regulate further dendritic growth and overlap (Huckfeldt et al., 2009; Reese, Raven, & Stagg, 2005), followed, in some cases, by additional passive displacements that in turn may degrade an initially ordered mosaic (e.g. Whitney, Raven, Keeley, & Reese, 2008).

5. How plastic is the acquisition of cellular morphology in the retina?

The recognition that visual cortical cells were conspicuously influenced by the visual environment during the early post-natal period, but that cells at earlier stages of the visual pathway appeared immune to these same effects (Daw & Wyatt, 1974; Wiesel & Hubel, 1963), led to the general presumption that sub-cortical structures lacked the capacity for plasticity, likely to be hard-wired during earlier development. The acquisition of cellular morphology within the retina was thought to be driven largely by cell-intrinsic developmental programs, and that the associated connectivity of individual cell-types required only appropriate process recognition to yield stratification and synaptogenesis within the plexiform layers, giving rise to the physiological properties of these cells. The past 25 years have witnessed a dramatic revision of this perspective, at least for certain types of retinal cells, following various studies showing that some cell-types undergo substantial morphological restructuring during early development, and that the mature properties of these cells' morphologies are critically dependent upon the presence of neighboring cells or upon the signals those cells transmit. Indeed, some of that plasticity has been shown to depend critically upon the visual environment itself. The following section will parse such “developmental plasticity” effects into those that regulate stratification, those that regulate dendritic overlap, and those regulate dendritic patterning

Regulation of stratification—Most mature retinal cell-types distribute their processes to restricted sub-strata within the plexiform layers. During development, however, some of these cell-types undergo a progressive restructuring of these axons or dendrites, rather than establishing their mature morphology through a steady, progressive transformation from a simple neuroblastic morphology. Some of this transformation is associated with the

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establishment of cellular positioning, either with respect to depth within the retina, or relative to homotypic neighbors, as discussed above; in other cases, such changes in morphology appear to take place independent of cellular migration or dispersion. For instance, after horizontal cells have migrated to their future position in the emerging inner nuclear layer, they exhibit an elaborate stellate dendritic morphology (figure 2) prior to stratifying within the outer plexiform layer (Huckfeldt et al., 2009;Reese et al., 2005). Curiously, the sole source of afferent innervation to their dendrites, the pedicles of the cone photoreceptors, stratifies within the outer plexiform layer ahead of this dendritic stratification by the horizontal cells, but the former are not required for the latter to reorganize, shown in coneless transgenic mice (Reese et al., 2005) or in transgenic mice in which all cones have been re-specified to acquire a rod fate (Raven, Oh, Swaroop, & Reese, 2007). The photoreceptors themselves have been shown to overshoot the developing outer plexiform layer in advance of its formation (figure 2) (Pow & Hendrickson, 2000), and in the ferret's retina, they extend as far as the inner plexiform layer before eventually retracting to the outer plexiform layer (Johnson et al., 1999). That this transient morphology might play some developmental role in the inner plexiform layer is suggested by the fact that these processes do not simply extend to the inner limiting membrane, but rather stratify in one of two sub-strata in the inner plexiform layer coincident with the processes of cholinergic amacrine cells (Johnson et al., 1999). They clearly recognize the latter to achieve this stratification, since ablation of the cholinergic amacrine cells disrupts this transient photoreceptor stratification (Johnson, Raven, & Reese, 2001).

The guidance for such stratification is likely mediated by cell-surface molecules that confer specificity (Honjo, Tanihara, Suzuki, Tanaka, Honda & Takeichi, 2000), and recent studies have identified candidates that mediate such heterotypic recognition in the inner plexiform layer (Yamagata & Sanes, 2008). One might expect that the earliest differentiating retinal cell-types in the inner retina should yield such laminar cues for other later-differentiating cells. It was therefore somewhat surprising that early ablation of the entire population of retinal ganglion cells (Williams et al., 2001) or of the cholinergic amacrine cells (Reese, Raven, Giannotti, & Johnson, 2001), two of the earliest generated cell-types in the inner retina (Reese & Colello, 1992) has, to date, yielded no conspicuous effect upon the organization of the inner plexiform layer. Unlike the cholinergic amacrine cells though, which exhibit a clear stratification nearly as early as these cells differentiate their processes within the inner plexiform layer (Reese et al., 2001; Stacy & Wong, 2003), at least some retinal ganglion cell types undergo a conspicuous reorganization of their dendritic fields within the inner plexiform layer, from an initially diffuse dendritic arbor to one that eventually stratifies within one, or two, discrete sub-strata in the inner (ON) or outer (OFF) portions of the inner plexiform layer (figure 2). Just how diffuse or non-specific that early morphology is has been contested (Bodnarenko, Jeyarasasingam, & Chalupa, 1995; Bodnarenko, Yeung, Thomas, & McCarthy, 1999; Coombs, Van Der List, & Chalupa, 2007; Lohmann & Wong, 2001; Maslim, Webster, & Stone, 1986; Stacy & Wong, 2003), but this developmental change appears to underlie a well-documented reduction in the proportion of retinal ganglion cells that respond to both the onset and offset of light (ON-OFF responses) (Tian & Copenhagen, 2001; 2003; Wang, Liets, & Chalupa, 2001). Furthermore, this morphological change is modulated by visual activity, as light deprivation reduces the proportion of mono-stratified dendritic fields and the proportion of ganglion cells showing only ON or OFF responses (see Tian, 2008, for review). Exactly how this effect is mediated is unclear: initial studies suggested that pharmacological blockade of ON-bipolar cell activation within the outer plexiform layer could mimic this effect of light deprivation (Bodnarenko & Chalupa, 1993; Bodnarenko et al., 1995) yet more recent studies silencing the output of these same ON-bipolar cells fails to disrupt stratification in the inner plexiform layer (Kerschensteiner, Morgan, Parker, Lewis, & Wong, 2009). Likewise, completely eliminating the cone afferents within the outer plexiform layer does not alter the dendritic

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stratification of either the horizontal cells (Reese et al., 2005) or the Type 7 cone bipolar cells (Keeley & Reese, 2010b), both normally post-synaptic to the cones.

Regulation of dendritic overlap—For post-receptoral retinal mosaics, each exhibits a characteristic degree of dendritic overlap for a given type of cell. Some cell-types extend their dendrites to the tips of homotypic dendritic fields, producing a tiling of the retinal surface (having a coverage factor of 1, indicating that every locus on the retina is subserved by the dendritic arbor of only a single cell of this type), while other cell-types overlap one another conspicuously, yielding a ten-fold or greater increase in coverage factor (see Reese, 2008a, for review). These type-specific differences are presumed to enable each cell type to mediate its unique functions within the retinal circuitry, and are thought to arise during development by homotypic interactions that constrain dendritic overlap. 25 years ago, a handful of experimental studies showed how the dendritic morphology of various retinal ganglion cell classes was influenced by interactions with neighboring ganglion cells, for instance, by biasing dendritic growth to one side of the field when neighboring cells on that same side were ablated (Eysel, Peichl, & Wässle, 1985; Hitchcock, 1989; Linden & Perry, 1982; Perry & Linden, 1982; Perry & Maffei, 1988), or by either increasing or decreasing the entire dendritic field following depletion or crowding of homotypic neighbors, respectively (Kirby & Chalupa, 1986; Leventhal, Schall, & Ault, 1988; Troilo, Xiong, Crowley, & Finlay, 1996). These early studies spawned the view that dendritic growth should be controlled by homotypic interactions, a view that was reinforced by subsequent imaging of filled pairs of cells during development–contacts were frequently present across overlapping dendritic arbors of homotypic neighbors (Lohmann & Wong, 2001). The fact that dendritic field size was found to increase as a function of eccentricity for most retinal cell classes, and that homotypic density often declines as a function of retinal eccentricity to yield a constant dendritic coverage (Wässle, Peichl, & Boycott, 1978), was regarded as further evidence that cell types other than ganglion cells also exhibited homotypic regulation of dendritic field size.

Recently this view has been tested directly for select types of retinal nerve cells in the mouse retina. For example, genetic depletion of homotypic neighbors has failed to show any evidence for such regulation of dendritic growth for either the melanopsin-positive retinal ganglion cells, or for the alpha-like neurofilament-rich (SMI-32) retinal ganglion cells (Lin, Wang, & Masland, 2004), two ganglion cell classes that achieve a coverage factor of between 1 and 2. Dopaminergic amacrine cells, having a greater dendritic overlap, on the order of 7 (figure 4a), also do not appear to regulate their dendritic morphology in relation to homotypic neighbors, although they may be susceptible to some heterotypic influence upon their dendritic field size (Keeley & Reese, 2010a). And cholinergic amacrine cells, perhaps the best-understood of all retinal cell-types requiring dendritic overlap to achieve their functionality (Zhou & Lee, 2008), exhibit a coverage factor around 30 in the mouse retina (figure 4b) but do not modulate their growth when the homotypic population is partially ablated during early postnatal development (Farajian, Raven, Cusato, & Reese, 2004; see also Keeley, Whitney, Raven, & Reese, 2007). Horizontal cells, by contrast, with a coverage factor of about 6 (figure 4c), show a conspicuous (two-fold) modulation of dendritic field area that is inversely related to homotypic cell density, evidenced by comparing strains that vary in horizontal cell number (Reese et al., 2005), or through genetic reduction in the normal population of horizontal cells (Poché, Raven, Kwan, Furuta, Behringer & Reese, 2008). Bipolars cells, having a dendritic coverage factor around 1 (figure 4d), achieve a tiling characteristic of some retinal ganglion cells (Wässle et al., 2009). Preliminary data suggest that this cell type is sensitive to homotypic neighbors, for genetic manipulations that increase or decrease the density of Type 7 cone bipolars yield correspondingly smaller versus larger dendritic field areas (Sammy Lee, unpub. obs.). For those cell types that do not evidence homotypic regulation of dendritic field growth in such manipulation studies, but

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have been shown to vary their dendritic field size as a function of retinal eccentricity, they presumably achieve such variation in dendritic growth through passive elongation driven by retinal expansion (Reese, 2008b), but other heterotypic signals may regulate their growth (Keeley & Reese, 2010a; Mehta & Sernagor, 2006).

The signaling between homotypic neighbors that regulate such interactions are relatively unexplored, but it is interesting to consider features of these cells' morphologies from this perspective: the dendritic fields of cone bipolar cells do not overlap, but they may share single pedicles (Wässle et al., 2009), suggesting that they colonize a field of pedicles by restraining further growth when confronting the dendritic field of a like-type cell, i.e. a simple contact-mediated inhibition of growth may be sufficient to define the approximate field area (figure 4d). Horizontal cells, on the other hand, extend dendritic fields that overlie one another more extensively, sharing pedicles with multiple neighboring cells throughout the dendritic field. The radius of their dendritic fields approximates the average near-neighbor distance (figure 4c), suggesting a cessation of dendritic growth triggered by interaction with neighboring somas, perhaps mediated by some threshold level of cell-surface molecule achieved on the soma itself, or a factor secreted from the soma locally.

There has been recent excitement about a prospective role played by the Down syndrome cell adhesion molecule, Dscam, in regulating homotypic dendritic repulsion, particularly as it is expressed in restricted populations of retinal neurons in the mouse retina (Fuerst, Koizumi, Masland, & Burgess, 2008; Fuerst, Bruce, Tian, Elstrott, Feller, Erskine, Singer & Burgess, 2009). In *Drosophila*, *Dscam* has thousands of alternatively spliced isoforms, giving single homotypic neighbors their own unique identity (Hattori, Chen, Matthews, Salwinski, Sabatti, Grueber & Zipursky, 2009). The neurites of these cells consequently engage in "self-avoidance", but freely overlap the dendritic fields of homotypic neighbors. If, however, these cells are engineered to express only one of these thousands of isoforms, then their processes exhibit both self-avoidance as well as homotypic avoidance with those from neighboring like-type cells (see Millard & Zipursky, 2008, for review). Curiously, in the mouse retina, while different cell types express Dscam, the mouse has only a single Dscam isoform, but rather than its mediating avoidance or repulsion between homotypic neighbors, it appears to mask an adhesive interaction: dopaminergic amacrine cells extend their dendrites in the wild-type mouse retina that appear oblivious to other dendrites from the same cell (e.g. figure 4a) or to dendrites from like-type cells in the vicinity (Keeley & Reese, 2010a), yet in the Dscam-mutant retina, the processes of these cells fasciculate in a manner never observed in the wild-type condition (Fuerst et al., 2008). Dscam, then, may provide a "non-stick" coating, preventing fasciculation that is itself specific to different cell-types (Fuerst & Burgess, 2009).

Interestingly, it is the cholinergic amacrine cell that differentiates a dendritic arbor that is most like the behavior expected by a genetic mechanism such as that above in *Drosophila* mediating self-repulsion yet permitting overlap with like-type neighbors. Cholinergic amacrine cells differentiate a dendritic arbor that approximates a space-filling function, dividing as a function of distance from the soma but rarely crossing over neighboring dendrites from the same cell. These cells establish such an immense degree of dendritic overlap with homotypic neighbors (figure 4b) that their growth would appear indifferent to them, while at the same time minimizing proximity to neighboring processes from the same soma. Models of morphogenesis that implement space-filling algorithms generate dendritic fields similar to those of real cholinergic amacrine cells (Sugimura, Shimono, Uemura, & Mochizuki, 2007), but the underlying signals generating this behavior, and how homotypic neighbors might be immune to cross-talk, remain to be determined.

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Regulation of dendritic patterning—Nearly 25 years ago, a number of studies examined the branching pattern of individual, intracellularly-labeled, retinal ganglion cells during early development. Many of these studies observed that these cells were often excessively branched before relinquishing many short processes to yield the more typical branch pattern observed in maturity (Dann, Buhl, & Peichl, 1987, 1988; Ramoa, Campbell, & Shatz, 1987, 1988). More recently, the dynamics of dendritic branching have been studied by labeling single cells in living retinas and examining the extension and retraction of processes during early development as they investigate the local environment. This motility of the processes of immature retinal ganglion cells has been shown to be influenced by synaptic transmission (Wong & Wong, 2000; 2001), as may be expected since such cells form contacts with heterotypic neighbors with which they ultimately secure synaptic contacts (Stacy and Wong 2003); such early communication may then participate in the stabilization of some branches and the elimination of others (see Wong & Ghosh, 2002, for review). Doubtless cell-intrinsic programs contribute to the distinctive dendritic branching patterns that discriminate different types of retinal ganglion cell from the earliest stages, and that may participate in their recapitulation *in vitro* (Montague & Friedlander, 1991), but the fine patterning within the dendritic field seems likely to depend upon afferent innervation and the activity those afferents convey. One of the most dramatic examples of afferent modulation of dendritic patterning comes not from a retinal ganglion cell though, but rather, the horizontal cell: these cells establish periodic clusters of dendritic terminal endings at each cone pedicle in the outer plexiform layer. In transgenic mice lacking all cones, their dendritic fields are largely barren of higher-order dendritic branches and clustered terminal endings, while in “conefull” mice (in which all of the rods are re-specified to become cones), their fields have hypertrophied, filling the entire field-area with branches that occupy the full depth of the outer plexiform layer (Raven et al., 2007; Reese et al., 2005). Dark-rearing does not reproduce the horizontal cell phenotype observed in the coneless mouse, but the *Cacna1f*-mutant mouse does, disrupting all synaptic transmission in the outer plexiform layer due to defective calcium channel assembly in the photoreceptor terminals (Raven et al., 2008). This developmental plasticity of the horizontal cell is all the more striking in the absence of similar changes in the other primary target of the cone pedicles in the outer plexiform layer, the cone bipolar cells (Keeley & Reese, 2010b). When considered in conjunction with the horizontal cell's exceptional capacity for remodeling in retinal degeneration (Lewis & Fisher, 2006) and its ability to re-enter the cell cycle and contribute to retinoblastoma (Ajioka et al., 2007), the plasticity of the horizontal cell appears to be unique amongst retinal nerve cells (Poché & Reese, 2009).

Development of the optic pathway

Over the past two decades, a multitude of factors have been shown to play a role in guiding optic axons to their target nuclei within the brain. Receding gradients of chondroitin sulfate proteoglycans (CSPGs) direct axonal growth radially toward the optic nerve head (Brittis, Canning, & Silver, 1992); cell-surface molecules promote fasciculation of later-arriving axons (Brittis & Silver, 1995; Ott, Bastmeyer, & Stuermer, 1998); Netrin signaling contributes to fiber entry into the optic stalk (Deiner, Kennedy, Fazeli, Serafini, Tessier-Lavigne & Sretavan, 1997); Slit proteins influence the positioning of optic axons as they arrive at the base of the brain (Plump, Erskine, Sabatier, Brose, Epstein, Goodman, Mason & Tessier-Lavigne, 2002); CSPGs contribute to the chronotopic reordering of optic axons as they enter the optic tract (Leung, Taylor, & Chan, 2003); and Slit and Semaphorin proteins provide directional signals further caudally within the optic tract (Atkinson-Leadbeater, Bertolesi, Hehr, Webber, Cechmanek & McFarlane, 2010). These and other factors that influence optic axonal growth and directionality have been reviewed elsewhere recently (Erskine & Thompson, 2008; Inatani, 2005; Sretavan, 2006; Xiao, Roeser, Staub & Baier, 2005). From a “systems” perspective, however, the most impressive advances during the

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past 25 years have been in our understanding of how the partial decussation is established at the optic chiasm, how retinotopic maps are created in target visual nuclei, and how separate ocular domains are produced within binocular visual structures.

6. How is the partial decussation established at the optic chiasm?

In the mammalian visual pathway, optic axons arising from ganglion cells in the ventro-temporal retina fail to decussate at the optic chiasm, projecting into the ipsilateral optic tract instead, thereby enabling binocular visual processing within each hemisphere without the need for inter-hemispheric connectivity. Fiber tracing studies showed that this uncrossed projection was not segregated from the crossing axons in some species, notably rodents and carnivores, thereby ruling out any simple account in terms of physical guidance (see Reese & Baker, 1992, Jeffery & Erskine, 2005, for reviews; but see also Jeffery, Levitt, & Cooper, 2008). Additionally, in most non-primate mammals, many cells in the temporal retina project contralaterally rather than ipsilaterally, complicating any simple “morphogenetic” account based upon retinotopic fiber order. Birthdating studies showed that the uncrossed component from the temporal retina was generated earlier than was the crossed temporal component (Dräger, 1985; Reese & Colello, 1992), while tract-tracing studies during development confirmed that the uncrossed component reached the brain prior to the crossed component (Baker & Reese, 1993; Godement, Salaun, & Mason, 1990; Sretavan, 1990). Other studies in carnivores confirmed that ganglion cell classes with partial decussation patterns were generated prior to, and gave rise to axons arriving earlier than, those with more complete decussations (Reese & Baker, 1990; Reese, Guillery, & Mallarino, 1992b; Reese, Guillery, Marzi, & Tassinari, 1991; Reese, Thompson, & Peduzzi, 1994; Walsh, Polley, Hickey, & Guillery, 1983). Together, these studies suggested that the factors that guide temporal optic axons to take an uncrossed course at the optic chiasm reflect a time-dependent signaling event in the chiasmatic region (Reese & Baker, 1992). While naturally occurring cell death and inter-ocular interactions have both been shown to influence the formation of the decussation pattern (Guillery, Mason, & Taylor, 1995; Linden & Reese, 2006), the primary mechanism appeared to be one of selective guidance.

Subsequent explant studies revealed a contact-mediated repulsion of outgrowing processes from ventro-temporal retina by cells of the chiasmatic midline region (Marcus, Blazeski, Godement, & Mason, 1995; Marcus & Mason, 1995; Wang, Dani, Godement, Marcus, & Mason, 1995). The midline cells were determined to be radial glia expressing the Ephrin-B2 ligand, deciphered by the presence of EphB1 receptor on the growth cones of temporal retinal axons, due to the restricted expression of *EphB1* within the ventro-temporal retina (figure 5) (Nakagawa Brennan, Johnson, Shewan, Harris & Holt, 2000; Petros, Shrestha, & Mason, 2009; Williams, Mann, Erskine, Sakurai, Wei, Rossi, Gale, Holt, Mason & Henkemeyer, 2003). That expression has been handsomely shown to be controlled by the transcription factor gene *Zic2*, which, when knocked down leads to a reduced uncrossed projection (Herrera, Brown, Aruga, Rachel, Dolen, Mikoshiba, Brown & Mason, 2003), and when ectopically expressed by nasal retinal cells leads to their upregulation of *EphB1* and *de novo* sensitivity in a repulsion assay (Lee, Petros, & Mason, 2008). *Zic2* is itself regulated by *Foxd1*, as *Foxd1*-knockout mice lose Zic2 and EphB1 proteins in the ventro-temporal retina, and fail to differentiate an uncrossed retinal projection from this same retinal region Together, these results suggest that a time-dependent modulation of *Zic2* expression may be sufficient to reduce EphB-mediated repulsion at the chiasmatic midline at progressively later developmental stages (see also Fabre, Shimogori, & Charron, 2010). Modulating the control of *Zic2* expression relative to the neurogenetic period may then account for the major species differences in decussation patterns, including the striking variability in the projection pattern for closely related species (Reese & Baker, 1990; Reese et al., 1991). It remains to be determined, however, whether the mechanisms generating the partial decussation in the

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mouse visual pathway bear relevance for other mammalian species, where there is a greater tendency for uncrossed axons to remain constrained to the temporal portion of the prechiasmatic nerve, and where early loss of one retina has little consequence upon the trajectory of optic axons from the remaining intact retina (see Jeffery et al., 2008).

These results also suggest that the well-documented abnormal decussation of temporal retinal axons at the optic chiasm in conditions that reduce ocular pigmentation (LaVail, Nixon, & Sidman, 1978; Rachel, Mason, & Beermann, 2002; Sanderson, Guillery, & Shackelford, 1974) may itself be mediated through the modulation of these upstream transcription factors. Explant studies have confirmed that the abnormality in oculo-cutaneous albinism lies within the retina itself, rather than within the chiasm (Marcus, Wang, & Mason, 1996),likely localized to the temporal retina (Rice, Goldowitz, Williams, Hamre, Johnson, Tan, & Reese, 1999), but the mechanism by which the cells of the pigmented epithelium behind the retina might influence these transcription factors regulating *EphB* receptor expression by retinal ganglion cells is still uncertain (Petros & Mason, 2008). The past 25 years have, however, seen new progress in understanding the signaling events within the cells of the retinal pigment epithelium (RPE). Like mutations in *tyrosinase*, producing the oculo-cutaneous phenotype and reductions in the size of the uncrossed projection due to ectopic crossing at the chiasmatic midline, so mutations in the *Oa1* gene that underlie ocular albinism also have smaller uncrossed projections (Incerti, Cortese, Pizzigoni, Surace, Varani, Coppola, Jeffery, Seeliger, Jaissle, Bennett, Marigo, Schiaffino, Tacchetti & Ballabio, 2000). Oa1 is a novel G-protein coupled receptor situated in the melanosomal membrane within RPE cells, with its N-terminal within the lumen of the melanosome and C-terminal within the cytoplasm (Schiaffino, Baschirotto, Pellegrini, Montalti, Tacchetti, De Luca & Ballabio, 1996). It may therefore serve as a sensor for some intra-melanosomal signal, acting through the G protein Gαi3 (Schiaffino, d'Addio, Alloni, Baschirotto, Valetti, Cortese, Puri, Bassi, Colla, DeLuca, Tacchetti & Ballabio, 1999), since *Gαi3* knock-out mice show, like *Tyr*−/− and *Oa1*−/− mice, abnormalities in their melanosomes and reductions in the size of their uncrossed pathways (Young, Powelson, Whitney, Raven, Nusinowitz, Jiang, Birnbaumer, Reese & Farber, 2008). These phenotypic similarities suggest a common signaling pathway that is initiated within melanosomes and which is defective in the absence of *tyrosinase* (Schiaffino & Tacchetti, 2005), perhaps the synthesis of L-dopa itself (Lopez, Decatur, Stamer, Lynch, & McKay, 2008).

7. How is the retinotopic map established within the optic tectum?

How the orderly representation of the retinal surface within central visual structures is established during development had been greatly debated 25 years ago. One camp was preoccupied with evidence supporting a “morphogenetic” account positing that the timing and/or spatial positioning of fibers as they grow along the pathway is critical for the formation of the retinotopic map (Horder & Martin, 1978). According to this view, the retinotopic ordering of optic axons present within the fiber pathway should be sufficient for ensuring their orderly termination within central targets (Bunt & Horder, 1983). Subsequent studies explored in great detail, particularly in mammals, the precision of such ordering, finding that any such order behind the eye appears to be largely a passive consequence of funneling fascicles of axons from the different quadrants of the retinal nerve fiber layer into the optic stalk (FitzGibbon & Reese, 1992, 1996), and, more critically, that such retinotopic fiber order becomes so degraded along the length of the optic nerve as to be nearly absent in the prechiasmatic portion of the pathway (Chan & Guillery, 1993; Horton, Greenwood, & Hubel, 1979; Reese & Baker, 1993; Simon & O'Leary, 1991; Williams, Borodkin, & Rakic, 1991; Williams & Rakic, 1985; but see also Jeffery et al., 2008), independent of the chronotopic reordering of axons that occurs pre-chiasmatically (Reese & Baker, 1992; Reese, 1994). Curiously, the dorso-ventral retinal axis regains some degree of retinotopic

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fiber order across the width of the optic tract, so that axons enter their target visual nuclei with some degree of pre-sorting in anticipation of the topographic mapping of this retinal axis (Chan & Guillery, 1993; Maggs & Scholes, 1986; Plas, Lopez, & Crair, 2005; Reese & Baker, 1993), but whether this pre-order contributes to map formation has yet to be determined. Axonal timing and pre-formed axonal scaffolds were likewise discounted as critical morphogenetic players (Cornel & Holt, 1992; Holt, 1991). Others had noted that topographic targeting errors were more common during early development, when the population of retinal ganglion cells undergoes naturally occurring cell death, leading to the suggestion that cell death might sculpt the topography from an initially disordered map (O'Leary, Fawcett, & Cowan, 1986). While cell death may act to eliminate some topographic targeting errors, it does not appear to play a major role in establishing the retinotopic map (Linden & Reese, 2006). Rather, targeted elaboration of a terminal field gradually emerges from axonal arbors that are initially diffuse, particularly in mammals (Yates, Roskies, McLaughlin, & O'Leary, 2001).

A second camp was largely made up of researchers favoring some form of chemospecificity underlying this mapping, as originally proposed by Sperry (1963). A major break-through came in 1987, when temporal retinal growth cones were shown to exhibit a clear preference when confronted with the option to elongate in the presence of membrane fragments from rostral versus caudal cells of the chick's optic tectum, using the *in vitro* "striped carpet assay" (Walter, Henke-Fahle, & Bonhoeffer, 1987b; Walter, Kern-Veits, Huf, Stolze, & Bonhoeffer, 1987a). Temporal axons were shown to avoid growth upon caudal membrane fragments, and the strength of this behavior varied as a function of rostro-caudal position upon the tectum. The membrane-linked molecules, Ephrin-A2 and Ephrin-A5, were subsequently identified to mediate this repulsion and to be expressed in an increasing rostro-caudal gradient, and were detected through a temporal-to-nasal gradient of declining EphA receptor expression upon the retinal ganglion cells (blue to yellow gradients in figure 6; (Cheng, Nakamoto, Bergemann, & Flanagan, 1995; Drescher, Kremoser, Handwerker, Cöschinger, Noda & Bonhoeffer, 1995). Subsequent studies have identified counter-gradients that may explain the preferential growth of nasal axons to the rostral tectum (Rashid, Upton, Blentic, Ciossek, Knöll, Thompson & Drescher, 2005); orthogonal retinal and tectal gradients mediated by Ephrin-B and EphB receptors that participate in the mapping of the dorso-ventral retinal axis across the lateral-to-medial tectal axis (Hindges, McLaughlin, Genoud, Henkemeyer, & O'Leary, 2002); and attractive rather than repulsive interactions mediating the effect of some of those gradients (red to green gradients in figure 6). These have been reviewed extensively recently (Clandinin & Feldheim, 2009; Flanagan, 2007; McLaughlin & O'Leary, 2005; Scicolone, Ortalli, & Carri, 2009); suffice it to say that complementary gradients across both retinal and tectal axes clearly participate in retinotopic map formation by providing retinal growth cones with the means to decipher positional identity upon the tectal surface. While some studies indicate a role for axonal interactions in the mapping mediated by Eph receptors (Brown, Yates, Burrola, Ortuño, Vaidya, Jessell, Pfaff, O'Leary & Lemke, 2000), others have suggested that neighboring ganglion cell axons are not critical for this targeting to the appropriate location upon the tectum (Gosse, Nevin, & Baier, 2008).

This is not to say that neighboring optic axons don't participate in the refinement of retinotopic precision as these axons establish their synaptic contacts with tectal cells. A role for correlated visual activity in the refinement of retinotopic mapping in the optic tectum was well-known 25 years ago (see Cline, 1991; Constantine-Paton, Cline, & Debski, 1990, for reviews). Perhaps one of the most significant collections of findings since then have been the demonstrations that, prior to photoreceptor maturation, inner retinal neurons are spontaneously active (Galli & Maffei, 1988); this activity is correlated between neighboring cells (Maffei & Galli-Resta, 1990); this correlated spontaneous activity travels across the

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retina as “waves” that emerge, traverse and then dissipate, creating a refractory period within the activated region in which subsequent wave-like activity is prohibited (Meister, Wong, Baylor, & Shatz, 1991; Wong, Chernjavsky, Smith, & Shatz, 1995; Wong, Meister, & Shatz, 1993); and that acetylcholine released from starburst amacrine cells plays a critical role in the lateral transmission of this wave-like activity (Feller, Wellis, Stellwagen, Werblin, & Shatz, 1996), as does glutamate released from bipolar cells (Blankenship et al., 2009; Wong, Myhr, Miller, & Wong, 2000) and gap junctional connectivity (Hansen, Torborg, Elstrott, & Feller, 2005; Syed, Lee, Zheng, & Zhou, 2004; Torborg, Hansen, & Feller, 2005), each operating during a distinct temporal window prior to the onset of photo-transduction in the outer nuclear layer and each operating with distinct kinetics (see Blankenship & Feller, 2010; Huberman, Feller, & Chapman, 2008, for reviews). The presence of such spontaneous patterned activity should ensure a correlation between the axonal arbors of neighboring retinal ganglion cells that may then participate in the refinement of their connectivity within target visual structures (figure 7).

That such spontaneous activity plays a role in retinotopic map refinement has been confirmed using mice in which nicotinic acetylcholine receptor function has been compromised by knocking out the β2-subunit: early studies reported that β2 knockout mice lack retinal waves entirely (Muir-Robinson, Hwang, & Feller, 2002; McLaughlin, Torborg, Feller, & O’Leary, 2003), but more recent studies have demonstrated that such mice show abnormally large and fast retinal waves (Sun, Warland, Ballesteros, van der List, Chalupa, 2008; Stafford, Sher, Litke, & Feldheim, 2009). Nevertheless, these mice have abnormally diffuse ganglion cell axonal arborizations in both the lateral geniculate nucleus and superior colliculus (Grubb, Rossi, Changeux, & Thompson, 2003; McLaughlin, Torborg, Feller, & O'Leary, 2003). These axons still target to their appropriate vicinity, mediated by the above-described Ephrin-A/EphA receptor signaling: knocking out the latter is known to disrupt retinotopic mapping, if not completely abolishing it (Feldheim et al., 2004), while doing so when also knocking out the β2-subunit of the nicotinic receptor near-completely abolishes retinotopic order (Pfeiffenberger, Yamada, & Feldheim, 2006). Indeed, the spontaneous activity not only refines the precision of these retinofugal maps, but also mediates the alignment of these maps between interconnected visual structures, including the projection from the visual cortex upon the superior colliculus (Triplett, Owens, Yamada, Lemke, Cang, Stryker & Feldheim, 2009).

8. How are the separate ocular domains established in the developing lateral geniculate nucleus?

The two hemi-retinas innervating the lateral geniculate nucleus terminate in discrete and complementary ocular territories. The patterning of these ocular domains is species-specific, commonly forming apposed laminae innervated by the opposite eyes, and in every species examined, arises during early development from an initially intermingled distribution of terminations from the two eyes (Jeffery, 1984; Linden, Guillery, & Cucchiaro, 1981; Marotte, 1990; Rakic, 1976; Shatz, 1983), wherein binocular innervation of single geniculate neurons is transiently present (Campbell & Shatz, 1992; Campbell, So, & Lieberman, 1984; Shatz & Kirkwood, 1984; Jaubert-Miazza, Green, Lo, Bui, Mills, & Guido, 2005). The fact that this segregation coincided with the period of naturally occurring ganglion cell loss suggested a causal relationship between the two events (Jeffery, 1984), but other studies examining the developmental change in the axonal arbors of single retinal ganglion cells revealed this process to be mediated by the selective pruning and elaboration of the terminal arbor (Sretavan & Shatz, 1984). The process was also shown to be dependent upon inter-ocular interactions, for early removal of one retina prevented the terminal field from the opposite eye to coalesce into its normal ocular domain (Jeffery, 1984; Rakic, 1981), and corrupted the normal sculpting of single axonal arbors (Sretavan & Shatz, 1986).

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Since then, the process by which these overlapping ocular projections segregate into separate ocular domains has been studied extensively, and debated vigorously. As this segregation occurs prior to the onset of visual activity, much attention has focused upon the possibility that, much as correlated spontaneous activity refines the precision of the retinotopic map in visual structures, so it should serve to ensure that activity patterns will be maximally distinct between axons arising from opposite eyes (figure 7). The first suggestion that activity played a role came from studies showing that pharmacological blockade of geniculate spiking by intracranial TTX injections prevented the normal sculpting of optic axons into their characteristically discrete terminal arbors (Sretavan, Shatz, & Stryker, 1988; but see). Subsequent work confirmed that spontaneous retinal activity was effective at driving geniculate activity (Mooney, Penn, Gallego, & Shatz, 1996), and that relative levels of such spontaneous retinal activity between the two eyes influenced the formation of ocular terminal fields in the lateral geniculate nucleus (Penn, Riquelme, Feller, & Shatz, 1998;Stellwagen & Shatz, 2002). Others then attempted to implicate the wave-like transmission of this spontaneous retinal activity by examining the above-mentioned β2-subunit knock-out mice (Muir-Robinson et al.,, 2002;Rossi et al., 2001), as well as connexin 36 knock-out mice, and in double knock-out mice (Torborg et al., 2005). Key to effective binocular segregation, apparently, is the presence the bursts of action potentials that are correlated between neighboring retinal ganglion cells, provided the frequency of such bursting is not so frequent to yield spurious correlations of activity between retinal ganglion cells at homonymous retinal loci in the two eyes (Butts, Kanold, & Shatz, 2007;Huberman, 2007;Torborg & Feller, 2005).

This summary simplifies the extensive debate recently aired on this topic (Chalupa, 2009; Feller, 2009). Doubtless further details of the critical role played by retinal activity in this process will be defined in the near future. But regardless of retinal waves, other additional factors are believed to play a role in this process, to account for the fact that the contralateral and ipsilateral ocular domains form in characteristic locations, and for the fact that animals with abnormal decussations at the optic chiasm produce ocular innervation of the lateral geniculate nucleus wherein the nasal and temporal retina still segregate to their characteristic portions (Guillery, 1974; Williams, Hogan, & Garraghty, 1994). As indicated above, there is a decreasing gradient of EphA receptor across the temporal to nasal retinal axis; there are as well gradients of Ephrin-A across the lateral geniculate nucleus (Feldheim et al., 1998; Huberman, Murray, Warland, Feldheim, & Chapman, 2005). Knocking out *Ephrin-A* expression in the lateral geniculate nucleus of the mouse, as well as overexpression of *EphA* within the retina of the ferret, disrupts the normal process of ocular segregation, consistent with the idea that the differential expression of EphA receptor in the temporal versus nasal retina (due to the normal declining gradient across this retinal axis) contributes to the targeting of these axons to distinct ocular domains (Huberman et al., 2005; Pfeiffenberger, Cutforth, Woods, Yamada, Rentería, Copenhagen, Flanagan & Feldheim, 2005). Alas, the similarities between these studies may be more superficial than at first examination, as the effect in the knock-out mouse yields erroneously positioned uncrossed terminal fields within the monocular segment of the lateral geniculate nucleus (that portion of the nucleus normally receiving only input from the far nasal retina viewing the monocular visual field), while *EphA* overexpression in the ferret retina yields primarily a failure of the ipsilateral and contralateral terminal fields to fully segregate within the binocular segment of the lateral geniculate nucleus (Huberman et al., 2005; Pfeiffenberger et al., 2005). These discrepancies need to be resolved before we can fully understand the relationship between the formation of ocularly-segregated retinotopic maps that are in binocular registration, and the role of activity in this process (Rebsam, Petros, & Mason, 2009). They are particularly vexing for our comprehension of the mapping of the uncrossed retinotopic projection, for this map's retinal axis runs counter to that for the crossed projection (i.e. the naso-temporal retinal axis for the crossed projection terminates across the lateral-to-medial axis of the LGN, while that

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for the uncrossed projection terminates across the medial-to-lateral axis). Should one of the EphA receptor gradients peak on the line of decussation, rather than at the far temporal periphery, and a declining Ephrin-A gradient be distributed across the axis of the lateral geniculate nucleus mapping the representation of the peripheral-to-central visual field, then the mouse may prove to construct its retino-geniculate mapping in a fashion comparable to that recently proposed for the human's visual pathway (Lambot, Depasse, Noel, & Vanderhaeghen, 2005). *Ephrin-A2/A5* double knock-out mice show disorderly uncrossed retino-tectal projections (Haustead, Lukehurst, Clutton, Bartlett, Dunlop, Arrese, Sherrard & Rodger, 2008), but the retino-tectal pathway may not be an appropriate model for understanding retino-geniculate organization, particularly with respect to ocular innervation patterns. For now, an adequate account of why the ipsilateral and contralateral ocular domains form where they characteristically reside still remains to be provided, as does an explanation for the polarity of the uncrossed map and the registration of the two half-retinal maps before the onset of vision.

Conclusions

The articles in that 25th Anniversary issue of *Vision Research* (like others in the present 50th Anniversary issue), described the rich theoretical issues in contemporary vision research then being addressed along with their biological underpinnings. A number of those issues had been the focus for study well before the founding of the journal, and, for a few of the authors writing at the time of the 25th Anniversary, seemed hardly closer to resolution. The subject matter described in the present chapter, in comparison, has a conspicuously different flavor to it, divorced entirely from visual function and relevant to understanding the development of the brain in general, being largely atheoretical in nature and subject to frequent revision in light of new discoveries every few years, focused on the life-history of the various components of the retina and optic pathway, and, where possible, on the genetic, molecular, cellular and activity-dependent mechanisms underlying those developmental changes. These studies inform us hardly at all about visual processing, but they better enable us to conceptualize the principles by which the mature organization comes about, and lead to the design of experiments attempting to validate those accounts, paving the way for further refinements in our understanding. Sperry would likely find the documented breadth of chemo-specific wiring within the nervous system entirely expected, but he would be astonished at the depth of our understanding of the causal chain of events underlying such interactions that produce the architecture and circuitry within the CNS mediating visually guided behavior.

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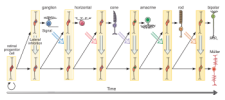

Figure 1.

Retinal progenitor cells are multipotent, competent to produce all types of retinal cell. This competence is progressively restricted, ensuring a unidirectional sequence of cell production, but not all progenitors at the outset of neurogenesis will produce each type of cell. At the left, early symmetrical divisions expand the population of progenitors. As their numbers increase, so do associated signals derived from them, eventually allowing proneural gene expression and Notch-Delta mediated lateral inhibition (vertical grey arrows) to permit only a subset of progenitors to leave the cell cycle (defining the onset of neurogenesis) and to differentiate. Newborn neurons provide signals (diagonal colored arrows) that restrict production of the same cell types, directing later-generated cells to subsequent fates. With the acquisition of additional cell types, so the micro-environment changes progressively (saturating vertical rectangles), and these extrinsic signals, coupled with intrinsic changes, alter the transcription factors expressed by progenitors as a function of time (colored nuclei). Thus changing cellular competence, intercellular signaling between progenitors, and secreted signaling by differentiating cells interact to yield variability in clonal constituency. The schematic implies a stem-like lineage tree, but by the insertion of additional divisions at various locations along this time-line, progenitors within this lineage tree may yield terminal divisions producing two postmitotic daughters (e.g. a ganglion cell and a cone photoreceptor, or a pair of horizontal cells, or a later-generated neuron and Muller glial cell, as shown at the far right), or daughters that both divide again, thereby amplifying the population of progenitors that produce later-generated cell types (e.g. rod photoreceptors and bipolar cells). (Modified from Agathocleous & Harris,2009).

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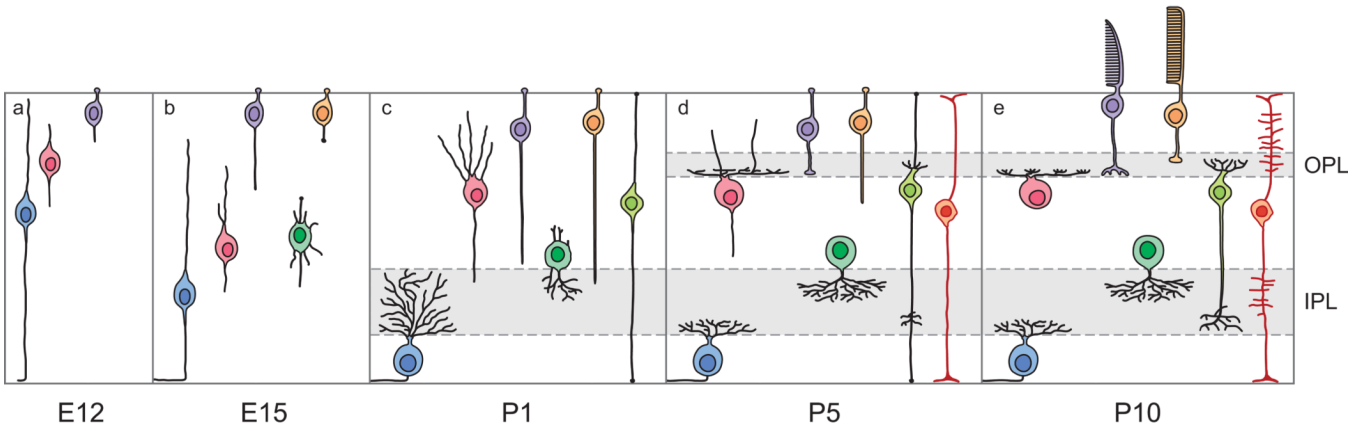

Figure 2.

Retinal precursors initiate a cell-type specific differentiation program, controlling their migratory behavior and their morphogenesis. Shown are five different developmental time-points, conveying these migratory and morphological distinctions as the different cell-types achieve their laminar positioning and adult morphologies. Cell type conventions as in figure 1. (Modified from Mumm & Lohmann, 2006).

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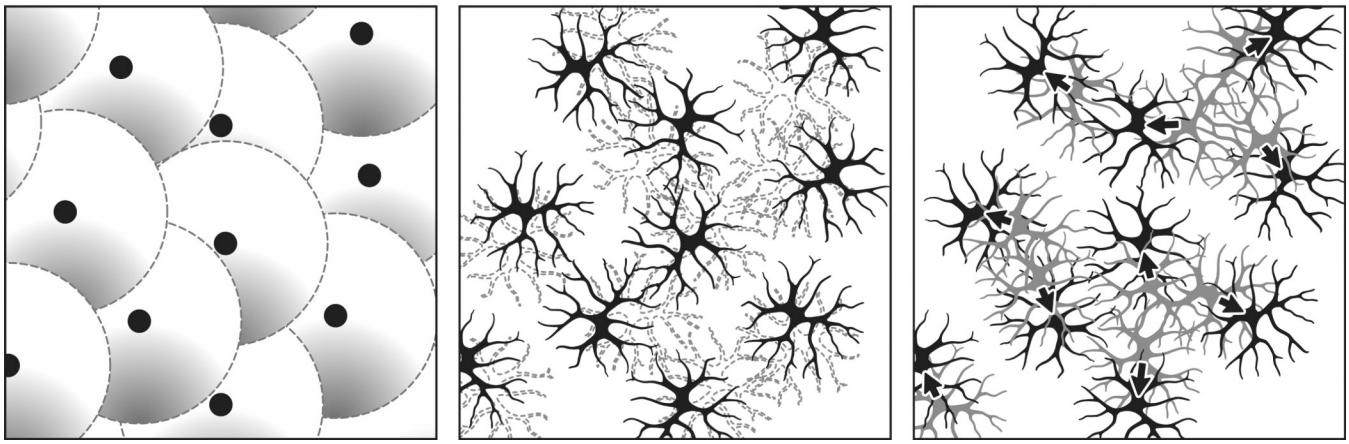

Figure 3.

The regularity of a retinal mosaic may be the product of distinct developmental events acting at different stages, dependent upon cell type. Periodic fate determining events may establish a regular pattern amongst a population of retinal precursors forming a retinal mosaic (a). At later stages during differentiation, naturally occurring cell death may eliminate closely positioned neighbors (dotted profiles in b), because of limited trophic support from afferents or targets. Mutual repulsion may also drive homotypic cells apart (arrows in c). (Modified from Reese, 2008b).

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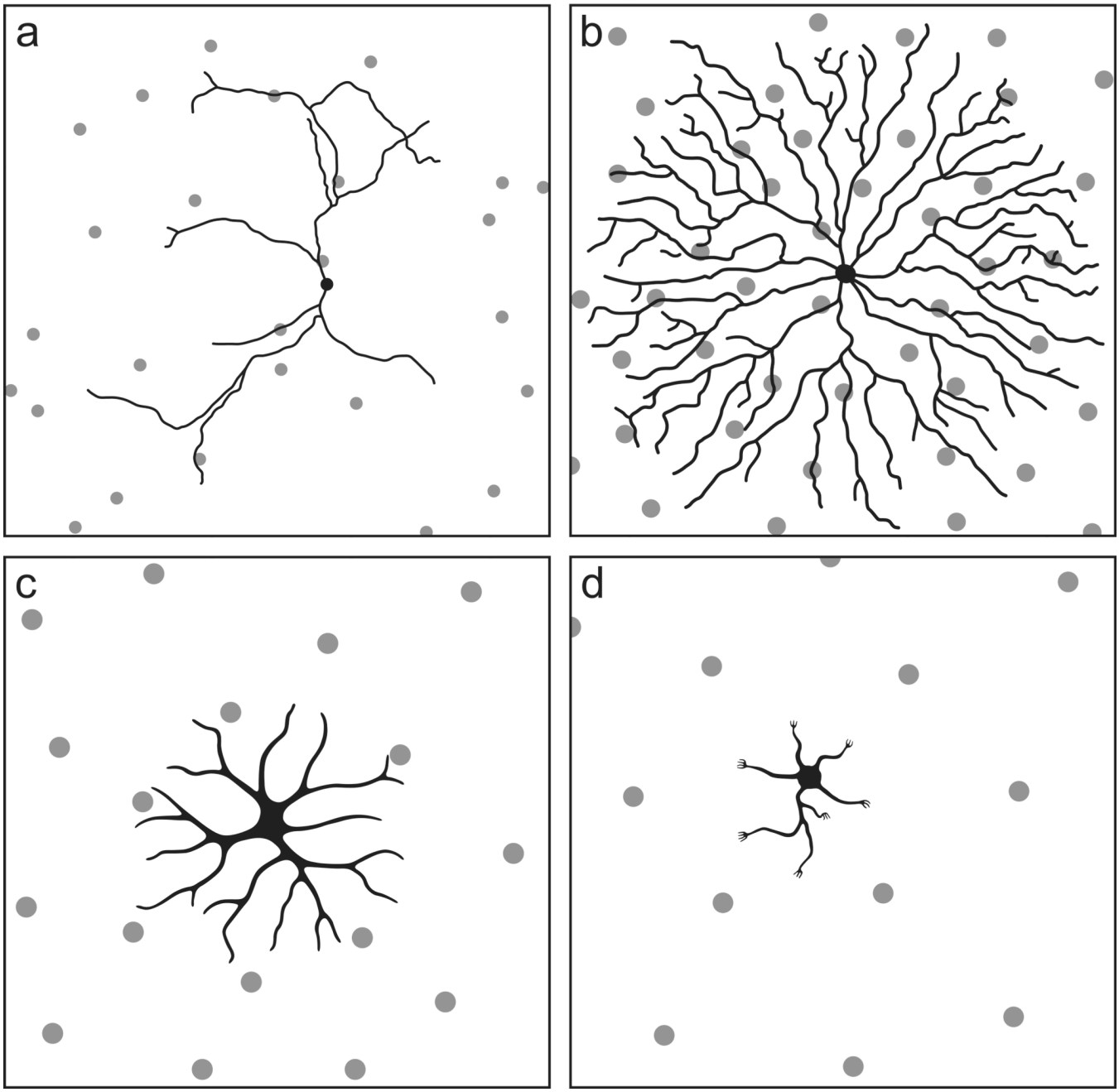

Figure 4.

The morphology of four different retinal cell types in relation to their retinal mosaics. a. Dopaminergic amacrine cells differentiate a dendritic arbor that is indifferent to the presence of other dendrites arising from the same cell as well as from those of homotypic neighbors. b. Cholinergic amacrine cells differentiate a dendritic arbor in which dendrites avoid one another, yet overlaps those of numerous homotypic neighbors. c. Horizontal cell somata constrain further dendritic outgrowth from their homotypic neighbors. d. Bipolar cell dendritic arbors achieve a tiling of the retinal surface, colonizing pedicles within their dendritic fields while also sharing those at the dendritic boundary with adjacent cells. The

panels are not drawn to the same scale, intending only to portray the relationship between morphology and homotypic density. (Modified from Reese, 2008b).

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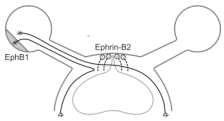

Figure 5.
The transcription factor Islet-2 represses *Zic2* expression, which in turn regulates *EphB1* receptor expression in the ventro-temporal retina. Ganglion cells in this region of the retina are therefore equipped to detect and respond to the presence of Ephrin-B2 on the surface of a select group of radial glia at the midline, deflecting these optic axons ipsilaterally. (Modified from Petros et al., 2009).

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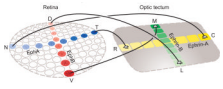

Figure 6.

Orthogonal density gradients of EphA3 and EphB2/EphB3 receptors upon the population of retinal ganglion cells enable their axonal growth cones to identify corresponding locations within the optic tectum by virtue of complementary Ephrin-A2/A5 and Ephrin-B1 gradients, mediating the establishment of the retinotopic map.

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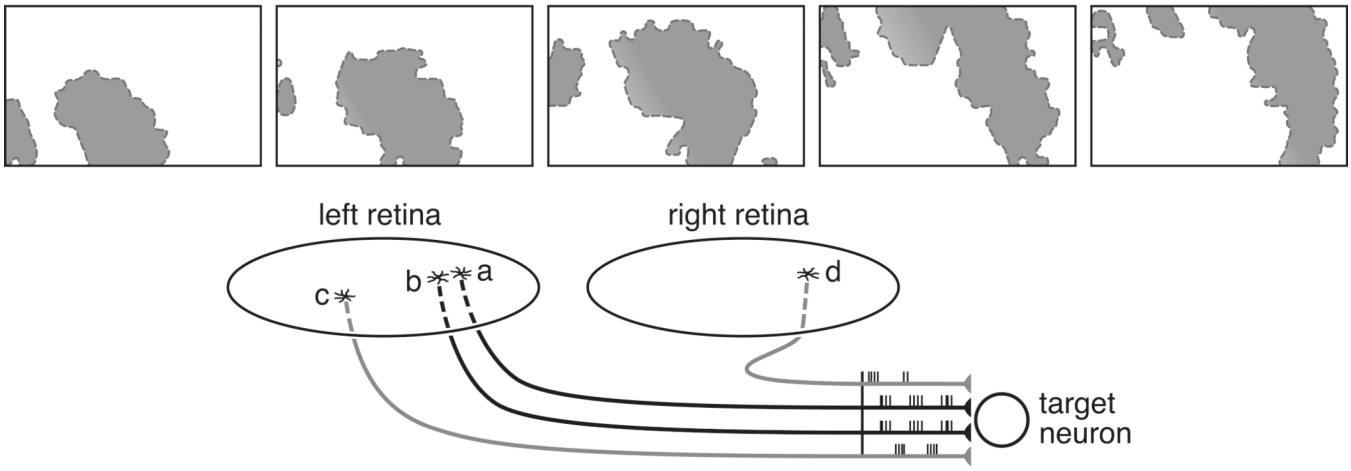

Figure 7.

Spontaneous (pre-visual) waves of activity spread across the surface of the developing retina (top), affecting each retina independently. The top five panels show the active regions (shaded) at two-second intervals from left to right. As a consequence, the bursts of action potentials by retinal ganglion cells will be more highly correlated between those axon terminals arising from adjacent locations on the retinal surface (a and b), ensuring a stabilization of their nascent synaptic contacts with target neurons, refining the precision of the retinotopic map (bottom). Much as more distant locations on the retina will have non-synchronous spontaneous activity with these two cells (c), so locations on the opposite retina should generate asynchronous discharges (d) relative to these cells, leading to the loss of binocular innervation upon single cells in the developing lateral geniculate nucleus. (Top modified from Stafford, Sher, Litke, & Feldheim, 2009).

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