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Prenatal development of axon outgrowth and connectivity

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Introduction

Understanding the developmental complexities of wiring the mammalian central nervous system (CNS) has driven many developmental neuro-biologists to seek simpler invertebrate nervous system models. Yet, it is still unclear how appli-cable simpler invertebrate model systems are to the problems of wiring complex mammalian circuits involving millions of neurons. One approach to the complexities of establishing connections in the mammalian CNS is to assume that the CNS be-comes appropriately wired through sequences of simpler mechanisms or rules. In this review we consider several such rules of development as they apply to early axon outgrowth and connectivity in the ferret visual system. The ferret has been used extensively as a model of mammalian visual sys-tem development because ferrets are relatively large mammals with well-developed visual sys-tems and give birth to large litters that are born at a very immature stage of development. In this re-view we restrict ourselves mainly to aspects of normal prenatal and early postnatal development of the ferret retina, lateral geniculate nucleus (LGN), visual cortex, and their connections, al-though aspects of the ontogeny of other systems and species are mentioned where relevant.

The mature ferret

The mature ferret retina contains a well-developed visual streak, an area centralis, and three physio-logically and morphologically defined ganglion cell classes (i.e., Y-cells with large somata, X-cells with medium somata, and W-cells with medium or small somata) (Henderson et al., 1988). As shown in Fig. 1, axons of nasal retinal ganglion cells of all three types cross the chiasm to innervate the LGN and other structures in the contralateral hemisphere. Most temporal retinal X-axons and some temporal retinal W-axons project to the ipsi-lateral hemisphere, but all temporal Y-axons cross (Vitek et al., 1985). Within the LGN, axons from each eye innervate separate layers; crossed axons terminate within layers A, C and C2 and uncrossed axons terminate in A1 and C1 (for simplicity we consider only the main layers of the LGN here). Within this framework, connections are further refined such that X and Y axons terminate within the A layers: layers that are, in turn, functionally subdivided into leaflets which receive afferents exclusively from either ON-center or OFF-center retinal ganglion cells (Stryker and Zahs, 1983). Y-axons also terminate in LGN layer C, and W-axons terminate within LGN layers C1 and C2. Thus, during normal development, retinogenicu-late axons of each class must find the correct target cells on the appropriate side of the brain and ter-minate retinotopically within the appropriate sub-division or layer of the LGN.

Assuming that the CNS of the adult ferret re-sembles that of the cat, axons emanating from all 3 classes of LGN cells terminate retinotopically within area 17, although a large number of Y LGN axons terminate in area 18, and area 19 receives projections mainly from W LGN cells (Hollander and Vanegas, 1977). Within area 17, LGN axons synapse principally on cells within layer IV. Thus, developing LGN cell axons are faced with many of
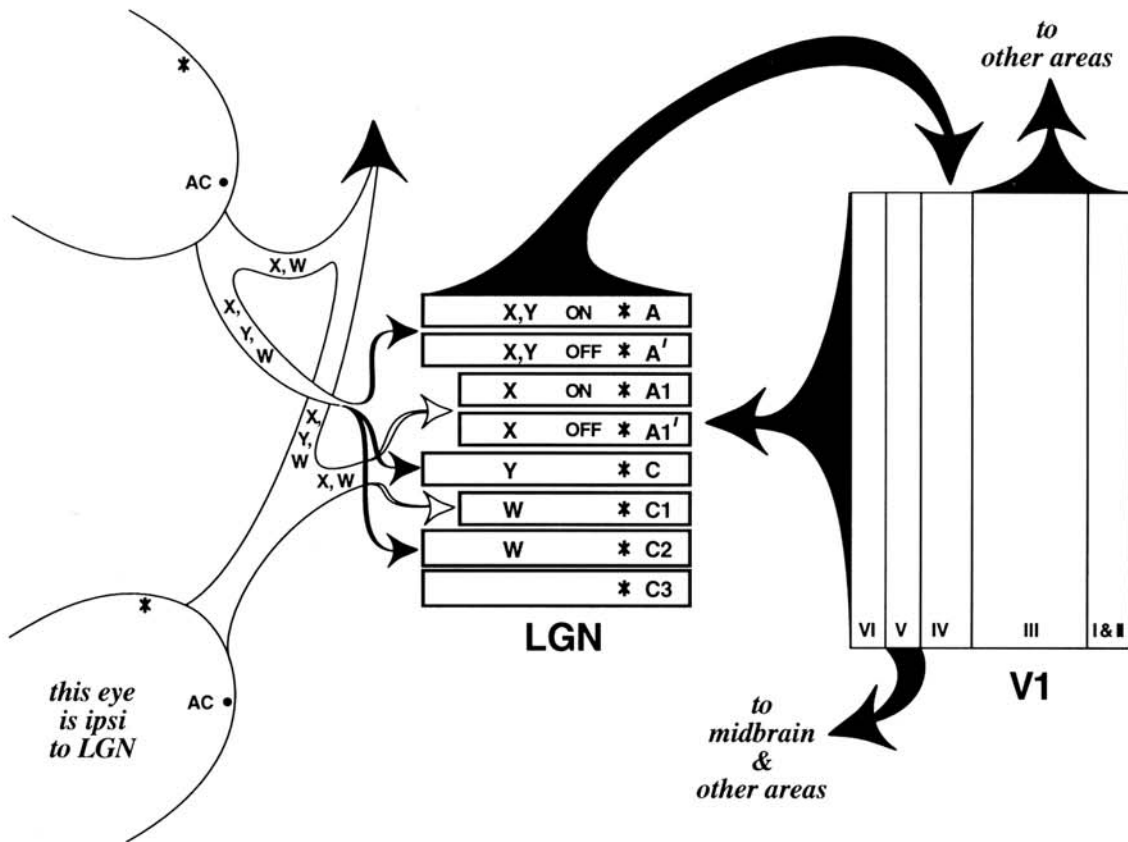
Fig. 1. A schematic diagram of the connections of the left and right eye with the left lateral geniculate nucleus (LGN) and the LGN with primary visual cortex (V1) in the adult ferret. Axons of nasal retinal ganglion cells of X, Y and W cells cross the chiasm to innervate the LGN and other structures in the opposite hemisphere. Most temporal retinal X-axons and some temporal retinal W-axons remain uncrossed projecting to the ipsilateral hemisphere, but all temporal Y-axons cross. Within the LGN, axons from each eye innervate separate layers such that crossed axons terminate within layers A, C and C2 and uncrossed axons terminate in A1 and C1. X and Y axons terminate within the A layers: layers that are, in turn, functionally subdivided into leaflets which receive afferents exclusively from either ON-center or OFF-center retinal ganglion cells. Y-axons also terminate in LGN layer C and W-axons terminate within LGN layers C1 and C2. C3 receives visual input from the superior colliculus. Within V1, LGN axons end principally on cells within layer IV. Cells in the cortical layers II/III project to other cortical areas, cells in layer V project principally to visual areas in the midbrain as well as visual areas in the thalamus and brainstem, and layer VI projects back to the LGN. Roman numerals indicate the cortical layers.

the same decisions as developing ganglion cell axons in that they must find the correct cortical target area, terminate within the correct layer of that area, and terminate upon specific cells within the layer to maintain retinotopic order.

As in other species, output cells in layers II/III of cortical area 17 send axons to other cortical areas, cells in layer V send axons to the midbrain and other subcortical targets, and cells in layer VI send axons back to the LGN (Rockland, 1985; Meissirel et al., 1993). The latter terminate retino-

topically, ending principally in the interlaminar zones between the main LGN layers (Claps and Casagrande, 1990). Again, as with retinal and LGN axon development, cortical axon development must involve a series of decisions in order to ensure that axons find their correct targets and maintain an orderly map within these targets. This brief sketch highlights examples of the order and complexity of normal adult geniculostriate connections. Establishment of correct and orderly connections requires that a large number of devel-
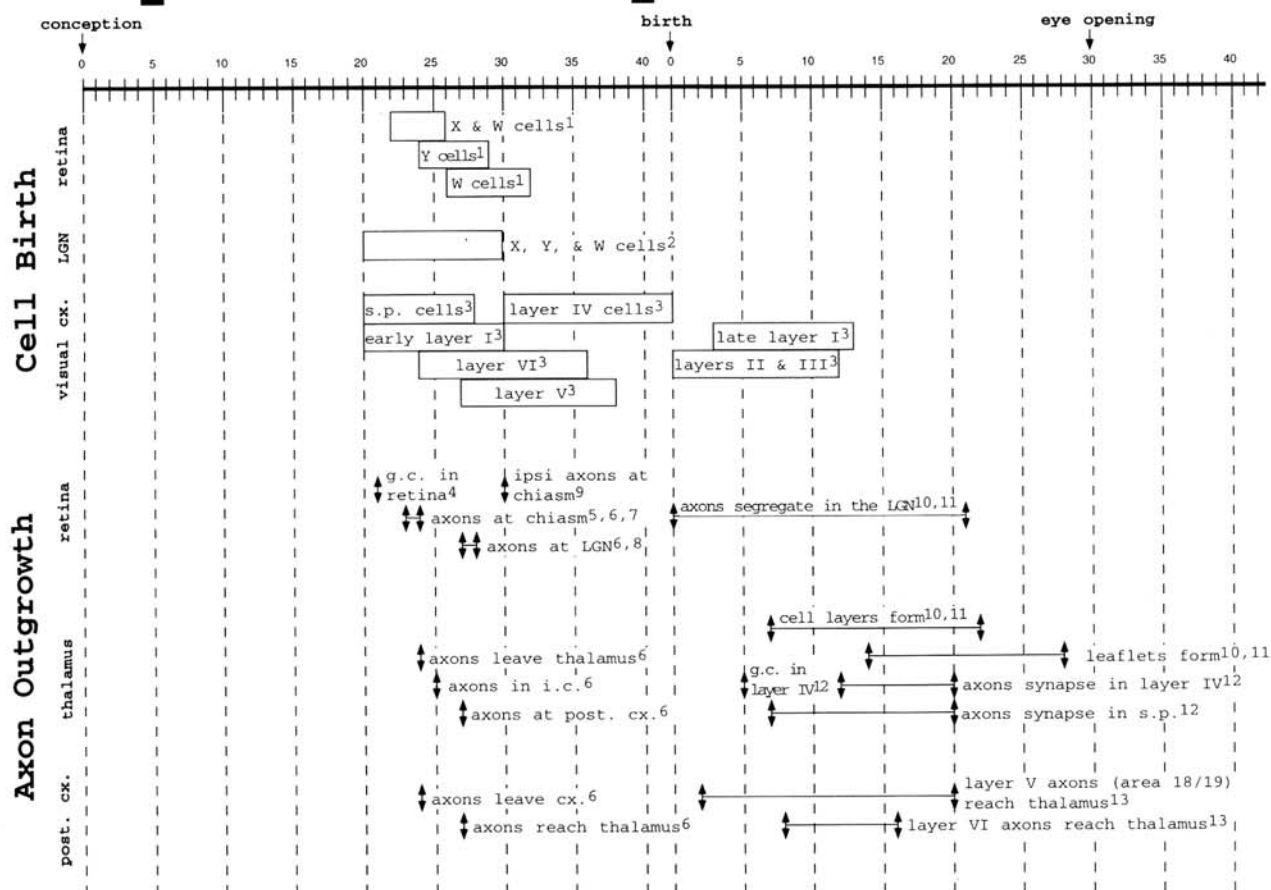
Days of Development in Ferret

Fig. 2. A chart showing the chronology of key events in the development of connections in the ferret visual system. Days of development from conception are indicated on the horizontal axis and times of cell birth (rectangles) and axon outgrowth (arrowheads) on the vertical axis. Conception and birth are represented as embryonic and postnatal day zero, respectively. Cx., cortex; G.c., growth cones; i.c., internal capsule; LGN, letral geniculate nucleus; post., posterior; s.p., subplate. References are as follows: 1, Reese et al. (1994); 2, Peduzzi (1989); 3, Jackson et al. (1989); 4, Greiner and Weidman (1981); 5, Taylor and Guillery (1994); 6, Johnson and Casagrande (1993); 7, Guillery and Walsh (1987b); 8, Cucchiario and Guillery (1984); 9, Baker and Reese (1993); 10, Linden et al. (1981); 11, Hutchins and Casagrande (1990); 12, Herrmann et al. (1994); 13, Clascá et al. (1996); 14, Mitrofanis, 1994a.

opmental decisions be made in a relatively short period of time. In the next sections, we consider some of the developmental factors that could play a role in these decisions.

Temporal coordination of early axon outgrowth

Temporal order has been shown in many systems to influence the development of cell phenotype (Reh and Kljavin, 1989; Bowerman et al., 1992). Thus, early born cells can influence the fate of later born cells as has been elegantly shown for the

development of cell phenotype in the *Drosophila* eye (Cagan, 1993; Kramer and Cagan, 1994). It has been more difficult to demonstrate the influence of temporal order on cell fate in more complex mammalian systems. However, even in these systems, to understand how axons make appropriate connections it is important to first know the temporal order of events. Fig. 2 summarizes what is currently known about the timing of cell birth and axon outgrowth in the developing ferret geniculostriate system throughout the 42-day gestation period and up to eye opening at day P30. Within

this system the first retinal ganglion cells, LGN cells, and area 17 cells are all "born" (i.e., have undergone their last cell division) at approximately the same time (E20-E22) (Jackson et al., 1989; Peduzzi, pers. commun., 1989; Reese et al., 1994). Moreover, the first axons grow out of these early cells almost immediately since axons are seen extending from cells in the retina, dorsal thalamus, and posterior cortex by E24 (Johnson and Casagrande, 1993; Taylor and Guillery, 1994).

Within the retina these early pioneering axons project ipsilaterally and develop from a transient population of dorsocentrally located retinal ganglion cells (Godemont et al., 1987; Colello and Guillery, 1990). Evidence from monocular enucleation studies indicates that these transient ganglion cells do not play a role in the chiasmatic choice of the permanent ipsilaterally projecting axons. Thus, the role of these early transient retinal axons remains to be defined. However, these axons could be responsible for providing signals that prepare the cellular/substrate environment for the axons which follow.

Within the retina, subsequent ganglion cells are born in a rough central to peripheral gradient beginning in the dorsocentral retina, nasal to the future area centralis (Henderson et al., 1988; Reese et al., 1994). Superimposed on this retinotopic gradient of maturation are differences in the chronological development of different functional classes of ganglion cells; medium ganglion cells (presumably X or medium W) begin to be generated (E22–E26) before the first large (Y) ganglion cells are born (E24–E29), which, in turn, begin to be generated before the smallest (W) ganglion cells are born (E26–E32) (Reese et al., 1994). As mentioned, ganglion cells send out axons right after they are born (perhaps even while they are migrating) since some of these axons have already reached and crossed the chiasm by E24 and some are present at the level of the dorsal thalamus by E27 (Guillery and Walsh, 1987b; Johnson and Casagrande, 1993; Taylor and Guillery, 1994). This means that early in development, the leading front of axonal growth cones from the eye is made up of a restricted subset of the total ganglion cell population from a roughly common retinal loca-

tion and a common ganglion cell class. Similarly, each subsequent front of axon growth cones that travel down the optic stalk, through the optic chiasm and into the optic tract represents a functional and topographic subset of the whole, although during the peak of ganglion cell birth and axon outgrowth a variety of growth cones are clearly present.

Less information is available for the development of the ferret LGN except that cells are generated between E20 and E30 (Peduzzi, 1989). In macaque monkeys, these cells divide at the ventricular zone and migrate laterally, presumably along radial glial cell processes that stretch from the ventricular surface to the pial surface of the diencephalon at this age (Rakic, 1977). It is unclear in the ferret whether cells in different LGN layers or functional classes are born at different times. However, in macaque monkeys, LGN cells of different layers/functional classes are born in sequence showing a lateral to medial gradient. Also in macaque monkeys, there is evidence that portions of the nucleus that will come to represent central vision mature first as evidenced by cell morphology, layer formation, and synaptogenesis (Rakic, 1977). Regardless, it is evident from comparisons of temporal sequences of ganglion cell birth, axon outgrowth, and LGN cell birth and maturation that early in development interactions involve more restricted populations (see also Casagrande and Brunso-Bechtold, 1985 for review). Thus, a subset of retinal axons have the potential to interact with the earliest born LGN cells right after the latter have been born.

Similarly, axons leaving from the region of the posterior thalamus develop early (E24) (Johnson and Casagrande, 1993). Moreover, there is evidence that the earliest axons from the thalamus might (as is the case in the retina) belong to a transient population of cells. These reticular/perireticular cells are born very early (prior to E25 in the ferret) and have been shown to form a network of cells that extend all the way to the cortical subplate (Mitrofanis, 1994a). In ferrets, major fiber bundles leaving from the thalamus are evident in the internal capsule by E25, and below the subplate of posterior cortex (visual cortex anlage)

by E27 (Johnson and Casagrande, 1993). As with retinal ganglion cells, some thalamic cells appear to send out axons soon after they are born. Moreover, if a gradient exists in the maturation of LGN cell classes or topographic regions of the nucleus itself in ferrets, then, as in retina, axons which will ultimately represent different parts of the visual field or different cell classes may arrive within cortex at slightly different times.

Within the cortex, evidence clearly shows that cells within the different layers, cells that will project to different locations, are born at different times. As in the retina and thalamus, the earliest born cortical neurons (E20–E26) belong to a transient population of cells that resides within the developing marginal zone (MZ) and the subplate (SP) (Jackson et al., 1989). Numerous articles have been written on the potential role of these cells in guidance of axons to and from the appropriate areas of cortex, so only a few points will be made in this review (see below and Shatz et al., 1988, 1990). Suffice it to say that these preplate cells are labeled from restricted placements of DiI within the dorsal thalamus of ferrets as early as E27. It is less clear how these early axons relate to the axon outgrowth from other layers of cortex since some axons will project subcortically to quite different targets and some will project to other cortical areas. Yet, all of these axons will pass through the subplate. Taken together, data on early axon outgrowth from the retina, thalamus, and cortex reveal some similar patterns. In each case, a population of early transient cells appears to be generated. The thalamic perireticular cells and cortical subplate cells have both been proposed to play roles as guidepost cells (Mitrofanis and Guillery, 1993); evidence does not support such a role for the earliest ganglion cells (Taylor and Guillery, 1994). Deletion of subplate cells in ferret cortex has been shown to cause axons to by-pass their targets in cortex, although other cues must guide axons to the location of their targets initially (Ghosh et al., 1990). Cells in the retina, LGN and cortex show clear gradients of cell birth that, in some cases, correlate with both mature topography and functional class. Thus, coarse topographic relationships may be established based simply upon these

chronological differences in maturation. Moreover, early growing axons encounter a different environment than those that follow, which, in turn, could account for differential axon guidance and targeting choices. Regardless, more detailed analysis of changes that occur at specific choice points and target zones over time will be required to ascertain the potential role of chronology in axon guidance.

The role of glia in axon guidance

A variety of mechanisms have been identified that can play a role in axon guidance. These mechanisms include differential adhesion to the substrate, general chemotropic and chemorepulsive factors, and special interactions with other cell types including glia, guidepost cells, and other axons (Stitt et al., 1991; Baier and Bonhoeffer, 1992, 1994; Fishman and Hatten, 1993; Baptista et al., 1994). All of these factors are likely to play a role in the guidance of retinogeniculostriate axons in the developing ferret.

In ferrets, glia have been suggested to play a role at several choice points in the visual pathway. Ferret optic axons undergo a major rearrangement as they pass from the optic nerve via the optic chiasm choice point to the optic tract. In the nerve, the axons gradually lose their original retinotopic/chronotopic order as they approach the chiasm. Just prior to the chiasm they reorganize into the chronotopic arrangement seen in the optic tract (Guillery and Walsh, 1987a). Guillery and Walsh (1987a) originally postulated that the changing glial environment between the nerve and the optic chiasm/tract can, in part, account for this rearrangement. In the nerve the glia exhibit an intrafascicular arrangement, whereas in the region of the chiasm, glia take on the radial arrangement common to the CNS. Guillery and Walsh (1987a) have argued that optic axon rearrangement can be explained if one assumes that axons arriving at the chiasm are initially guided by radial glia toward the pial surface. In addition, the glia (or specialized neurons (see below) within the chiasm) appear to provide other axon guidance clues since removal of one eye prevents the non-transient ipsilaterally

projecting axons from crossing the chiasm (see for review Taylor and Guillery, 1994; Guillery et al., 1995). When early developing ferret or rat retinal axons are labeled via carbocyanine dye (DiA or DiI) placed in the optic cup, these dyes move transcellularly to label chiasmatic glia as well as axons from the opposite eye (Johnson and Casagrande, 1991). Such transcellular labeling is evident as soon as retinal axons reach the chiasm but is not evident in the chiasm after the pathway has matured postnatally suggesting that retinal axons may have specialized contacts with midline glia early in development. Chiasmatic glia are also known to transiently express several unique epitopes including the calcium-binding protein lipocortin 1 (LC1) and stage-specific embryonic antigen 1 (SSEA 1), both of which have been suggested to play a role in axon guidance (McKanna, 1992; Marcus et al., 1995). Moreover, in mice, ventral temporal retinal axons which normally project ipsilaterally avoid membranes made up of chiasmatic cells indicating that these axons receive an inhibitory signal from the midline (Wizenmann et al., 1993).

After ferret retinal axons have crossed the chiasm they also may communicate with radial glial cells since DiA-labeled retinal axons appear to transfer label to radial glial cells as they grow along the surface of the diencephalon (Johnson and Casagrande, 1993). When these axons arrive at anlage of the LGN, they are in a position to follow local radial glial guides and potentially meet with LGN neurons using the same glial processes; as mentioned above, LGN neurons are proposed to migrate along these same radial glia from the ventricular zone to the LGN anlage at the lateral edge of the diencephalon (Rakic, 1977).

Within the LGN itself, glia could have an additional role in cellular lamination since astrocytes labeled with antibodies to glial intermediate filaments (GFAP or vimentin) form transient bands within the incipient interlaminar zones in ferrets (Hutchins and Casagrande, 1990). These interlaminar zones also transiently contain high levels of fibronectin (Brunso-Bechtold et al., 1992) and 3-fucosyl-*N*-acetyl-lactosamine (FAL), which is thought to represent a functionally active carbohydrate moiety of a cell adhesion molecule on a subclass of astrocytes (Mavity-Hudson et al., 1991). FAL is likely the same as SSEA-1 or CD15 (Bartsch and Mai, 1991). In addition, the incipient LGN interlaminar zones in ferrets transiently express a keratin sulfate proteoglycan which is associated with astrocytes and is known to block neuronal attachment and axon outgrowth in culture (Robson and Geisert, 1994).

Concerning connections between diencephalon and telencephalon, it is unclear whether intrafascicular glia guide axons between these structures, although such glia have been identified within the developing internal capsule (unpublished observations). Studies by Norris and Kalil (1991) certainly implicate radial glia in guiding developing axons into the cortical plate after they have arrived in cortex. In the diencephalon, corticothalamic axons could also make use of radial glial guides as they approach their targets, but there is no direct evidence that this is the case at present.

The role of neurons in axon guidance

Retinal, LGN, and cortical axons are presumably guided toward their initial target areas (e.g., diencephalon or telencephalon) by a combination of general permissive and instructive pathway cues, but specific instructions likely occur at the chiasm, perireticular nucleus, and the cortical subplate. As mentioned above, unique transient populations of neurons exist at axon pathway choice points. In mice (similar studies have not been done in ferrets), deletion of the transient population of hypothalamic neurons that predate the formation of the chiasm causes retinal axons to stall at the chiasm (Sretavan et. al., 1995). These prechiasmatic neurons express cell surface molecules that have been implicated in axon guidance including L1, a member of the immunoglobin superfamily which has been shown to promote axon outgrowth in culture, and CD44, a glycoprotein which binds to the extracellular matrix (Lemmon et al., 1989; Aruffo et al., 1990). However, it is not yet clear how the presence of these cells or the molecules they express actually influence the behavior of retinal axons.

In the diencephalon of ferrets, transient reticular and perireticular cells could play key roles in guiding both thalamocortical and corticothalamic axons. Axons connecting the cortex and thalamus show clear rearrangements within the region of the perireticular nucleus suggesting this nucleus plays some role in axon pathfinding (Mitrofanis and Guillery, 1993). Moreover, within the diencephalon, the ferret LGN anlage receives its earliest axonal projections (E23) from transient reticular nucleus neurons (Mitrofanis, 1994b). In ferrets, the transient reticular nucleus neurons are arranged continuously with the early born perireticular neurons which, in turn, appear continuous with cortical subplate cells (Mitrofanis, 1994a). Since corticofugal axons also form junctions with perireticular cells (Ramcharan et al., 1995), it may be that the earliest highway between thalamus and cortex is formed by connections between transient reticular cells, perireticular cells, and subplate cells as illustrated schematically in Fig. 3.

Efforts to label corticogeniculate axons postnatally in ferrets reveal that these axons are sparse in the LGN before P11, and are very immature in morphology even at P14 (Claps and Casagrande, 1990). The latter results indicate that corticogeniculate axons wait at some location outside of the LGN before entering, possibly in the primordial reticular/perireticular zone. However, the first wave of corticogeniculate axons could also be transient residents arising from subplate cells that are subsequently eliminated as proposed by McConnell et al. (1989). In the latter case, one could postulate that the first connections are actually made between cortical and subcortical populations of early born transient cells and that permanent axons actually do not "wait" before growing into their targets. Instead, the "waiting" period is a period during which early transient populations form a scaffold of connections to be followed by permanent axons. In fact, a very recent study of corticothalamic axon development in ferrets argues that the earliest cells projecting to the LGN arise from pyramidal cells in layer V at birth (E42) and that cells in layer VI and the subplate do not project to the thalamus until 8–10 days postnatal (Clascá et al., 1996). These results con-
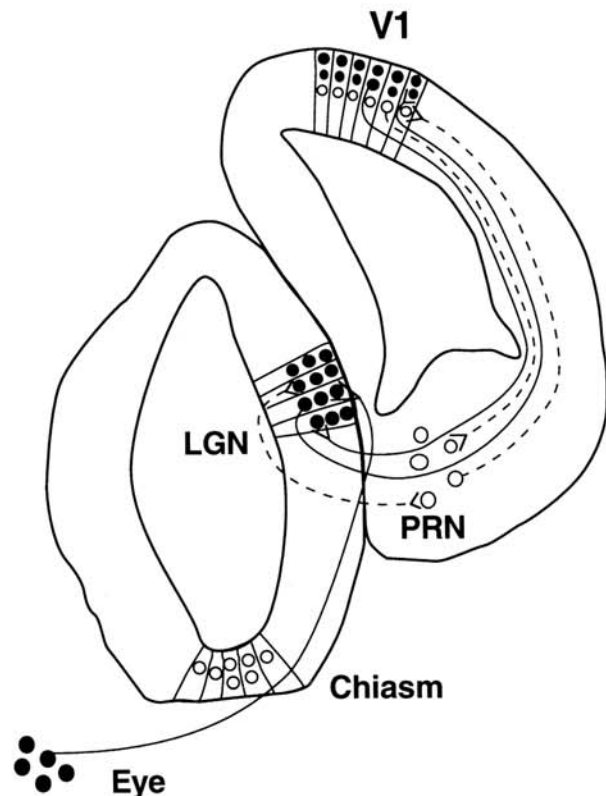

Fig. 3. A schematic diagram showing early transient cell groups (open circles) and their connections (dashed lines) and permanent cell groups (black circles) and their connections (solid black lines) in the ferret retinogeniculostriate system. Only permanent crossed connections from the eye are shown. Axons from the eye receive guidance cues from either transient cells or radial glial cells in the optic chiasm. Transient connections between the thalamus and cortex may originally form as a scaffold of connections between transient cells in the reticular nucleus (RN) and perireticular nucleus (PRN) of the thalamus and subplate of primary visual cortex (V1). Permanent axons connecting the lateral geniculate nucleus (LGN) and cortex could use the transient scaffold as a guide to their proper destinations; other local cues from radial glia and neurons could then guide axons into their targets. See text for details.

flict with results of earlier studies in fetal ferrets and cats (McConnell et al., 1989; Johnson and Casagrande, 1993). Both of the latter studies provide evidence that axons leave the visual cortex and enter the thalamus more than a week and a half earlier (see Fig. 2). One possibility is that the earlier axons are, in fact, the axons of the early born subplate cells. (The "subplate cells" identified

by Clascá et al. (1996) may actually represent permanent white matter cells or displaced layer VI cells). The actual subplate cells may only extend axons as far as the reticular nucleus (see earlier discussion), an area that may have been included in the thalamic DiI placement sites of the McConnell et al. (1989) and Johnson and Casagrande (1993) studies but not in the study by Clascá et al. (1996). Such an interpretation would also fit with findings of Claps and Casagrande (1990) showing that few individual cortical axons can be traced to the LGN in ferrets prior to P11.

Refinement of connections

Although the purpose of this chapter is to consider rules of early axon outgrowth and pathfinding, it is appropriate to briefly consider factors that refine axonal connections within the ferret visual system. Axons within the retinogeniculostriate system go through early and late growth programs that share several features in common.

Retinal, cortical and thalamic axons begin to innervate targets by sending simple side branches into the target region. Initially, additional transient side branches may also extend into zones (e.g. several visual nuclei) which will not be innervated by these axons in adults (Jhaveri et al., 1991; Ghosh and Shatz, 1992). Further refinement appears to involve a similar process in which the correctly targeted side branches now put out a number of simple short branchlets some of which are also transient (Sretavan and Shatz, 1986). Finally, the appropriate side branchlets are expanded and elaborated.

It appears from work in several species that the initial targeting and establishment of crude topographic connections between the retina, LGN, and visual cortex do not require neural activity (Cullen and Kaiserman-Abramof, 1976; Brunso-Bechtold and Casagrande, 1981; Guillery et al., 1985). Guidance to the target clearly involves a number of factors some of which were considered above. However, several late developing axonal refinements, which all occur postnatally in ferrets, do appear to depend upon neural activity. These axonal events include the segregation of retinal axons

into eye specific layers within the LGN, formation of ocular dominance bands in cortex, and refinement of lateral connections between cortical columns (Stryker and Harris, 1986; Shatz and Stryker, 1988; Callaway and Katz, 1991). In fact, normal cortical ocular dominance columns and possibly tangential connections among orientation columns depend not only on neural activity, but also on useful patterned visual activity (Wiesel and Hubel, 1963; Blakemore, 1976; Wilson et al., 1977; Chapman et al., 1986). Additionally, many of these activity-dependent refinements appear to involve competition between retinotopically overlapping populations and Hebbian mechanisms designed to allow cells which fire together to synapse together (Bliss and Collingridge, 1993; Glanzman, 1994; Kirkwood and Bear, 1994; Obermayer et al., 1995). In the ferret LGN, segregation of axons from ON- and OFF-center ganglion cells into appropriate LGN sublayers also appears to require activity. This dependence on activity has been demonstrated by blockade of NMDA receptors which would presumably disrupt mechanisms designed to detect temporal correlations between retinal axon activity and LGN cell activity (Hahm et al., 1991; Mooney et al., 1993; Smetters et al., 1994). The latter finding is curious since the segregation of ON- and OFF-center axons occurs between P17 and P28 prior to eye opening in ferrets at P30. Thus, this Hebbian mechanism must normally operate without visual input except perhaps via diffuse light/dark stimulation through the eyelids.

Conclusions

The early development of connections within the ferret visual system involves a series of steps designed to ensure that axons find appropriate retinotopically correct targets. Retinal, thalamic, and cortical axons within this system go through similar steps in development which suggest that common principles may apply. In all three cases, the earliest pioneering axons arise from transient populations of cells in the retina, reticular/perireticular nucleus of the thalamus, and cortical subplate, respectively. It is possible that each of

these populations plays a role in the guidance of the permanent axons that follow, but evidence of such a role has only been obtained so far for cortical subplate cells. The permanent axons grow out in an orderly fashion suggesting that subsequent relationships between axons and targets may be influenced by chronology. Thus, in regions such as the optic chiasm or LGN, different waves of retinal axons may encounter different environments since cues at specific choice points and the relative maturity of target cells may differ. Permanent axons may be guided to their individually specific targets by radial glial cells. The latter are not only in a position to guide axons, but also to align axons with target cells within a topographic column. However, the exact roles of radial glia with respect to retinal, thalamocortical, and corticothalamic axon pathfinding remains to be defined. Finally, once rough topographic connections have been established within the ferret visual system, fine tuning of connections appears to depend upon neural activity.

Acknowledgments

References

Aruffo, A., Stamenkovic, I., Melnick, M., Underhill, C.B. and Seed, B. (1990) CD44 is the principal cell surface receptor for hyaluronate. *Cell*, 61: 1303–1313.

Baier, H. and Bonhoeffer, F. (1992) Axon guidance by gradients of a target-derived component. *Science*, 255: 472–475.

Baier, H. and Bonhoeffer, F. (1994) Attractive axon guidance molecules. *Science*, 265: 1541–1542.

Baker, G.E. and Reese, B.E. (1993) Chiasmatic course of temporal retinal axons in the developing ferret. *J. Comp. Neurol.*, 330: 95–104.

Baptista, C.A., Hatten, M.E., Blazeski, R. and Mason, C.A. (1994) Cell-cell interactions influence survival and differentiation of purified Purkinje cells in vitro. *Neuron*, 12: 243–260.

Bartsch, D. and Mai, J.K. (1991) Distribution of the 3-fucosyl-*N*-acetyl-lactosamine (FAL) epitope in the adult mouse brain. *Cell Tissue Res.*, 263: 353–366.

Blakemore, C. (1976) The conditions required for the maintenance of binocularity in the kitten's visual cortex. *J. Physiol.*, 261: 423–444.

Bliss, T.V. and Collingridge, G.L. (1993) A synaptic model of memory: long-term potentiation in the hippocampus. [Review]. *Nature*, 361: 31–39.

Bowerman, B., Tax, F.E., Thomas, J.H. and Priess, J.R. (1992) Cell interactions involved in development of the bilaterally symmetrical intestinal valve cells during embryogenesis in *Caenorhabditis elegans*. *Development*, 116: 1113–1122.

Brunso-Bechtold, J.K. and Casagrande, V.A. (1981) Effect of bilateral enucleation on the development of layers in the dorsal lateral geniculate nucleus. *Neuroscience*, 6: 2579–2586.

Brunso-Bechtold, J.K., Agee, D. and Sweatt, A.J. (1992) Immunohistochemical evidence for transient expression of fibronectin in the developing dorsal lateral geniculate nucleus of the ferret. *J. Comp. Neurol.*, 315: 275–286.

Cagan, R. (1993) Cell fate specification in the developing *Drosophila* retina. *Development* (Suppl.): 19–28.

Callaway, E.M. and Katz, L.C. (1991) Effects of binocular deprivation in the development of clustered horizontal connections in cat striate cortex. *Proc. Natl. Acad. Sci. USA*, 88: 745–749.

Casagrande, V.A. and Brunso-Bechtold, J.K. (1985) Development of lamination in the lateral geniculate nucleus: critical factors. In: R. Aislin (Ed.), *Advances in Neural and Behavioral Development*, Vol. 1. Ablox, Norwood, pp. 33–78.

Chapman, B., Jacobson, M.D., Reiter, H.O. and Stryker, M.P. (1986) Ocular dominance shift in kitten visual cortex caused by imbalance in retinal electrical activity. *Nature*, 324: 154–156.

Claps, A. and Casagrande, V.A. (1990) The distribution and morphology of corticogeniculate axons in ferrets. *Brain Res.*, 530: 126–129.

Clascá, F., Angelucci, A. and Sur, M. (1996) Layer-specific programs of development in neocortical projection neurons. *Proc. Natl. Acad. Sci. USA*, in press.

Colello, R.J. and Guillery, R.W. (1990) The early development of retinal ganglion cells with uncrossed axons in the mouse: retinal position and axonal course. *Development*, 108: 515–523.

Cucchiaro, J. and Guillery, R.W. (1984) The development of the retinogeniculate pathways in normal and albino ferrets. *Proc. R. Soc. London, Ser. B: Biol. Sci.*, 223: 141–164.

Cullen, M.J. and Kaiserman-Abramof, I.R. (1976) Cytological organization of the dorsal lateral geniculate nuclei in mutant anophthalmic and postnatally enucleated mice. *J. Neurocytol.*, 5: 407–424.

Fishman, R.B. and Hatten, M.E. (1993) Multiple receptor systems promote CNS neural migration. *J. Neurosci.*, 13: 3485–3495.

Ghosh, A. and Shatz, C.J. (1992) Pathfinding and target se-

lection by developing geniculocortical axons. *J. Neurosci.*, 12: 39–55.

Ghosh, A., Antonini, A., McConnell, S.K. and Shatz, C.J. (1990) Requirement for subplate neurons in the formation of thalamocortical connections. *Nature*, 347: 179–181.

Glanzman, D.L. (1994) Postsynaptic regulation of the development and long-term plasticity of Aplysia sensorimotor synapses in cell culture. *J. Neurobiol.*, 25: 666–693.

Godement, P., Vanselow, J., Thanos, S. and Bonhoeffer, F. (1987) A study in developing visual systems with a new method of staining neurones and their processes in fixed tissue. *Development*, 101: 697–713.

Greiner, J.V. and Weidman, T.A. (1981) Histogenesis of the ferret retina. *Exp. Eye Res.*, 33: 315–332.

Guillery, R.W. and Walsh, C. (1987a) Changing glial organization relates to changing fiber order in the developing optic nerve of ferrets. *J. Comp. Neurol.*, 265: 203–217.

Guillery, R.W. and Walsh, C. (1987b) Early uncrossed component of the developing optic nerve with a short extracerebral course: a light and electron microscopic study of fetal ferrets. *J. Comp. Neurol.*, 265: 218–223.

Guillery, R.W., LaMantia, A.S., Robson, J.A. and Huang, K. (1985) The influence of retinal afferents upon the development of layers in the dorsal lateral geniculate nucleus of mustelids. *J. Neurosci.*, 5: 1370–1379.

Guillery, R.W., Mason, C.A. and Taylor, J.S. (1995) Developmental determinants at the mammalian optic chiasm. *J. Neurosci.*, 15: 4727–4737.

Hahm, J.O., Langdon, R.B. and Sur, M. (1991) Disruption of retinogeniculate afferent segregation by antagonists to NMDA receptors [see comments]. *Nature*, 351: 568–570.

Henderson, Z., Finlay, B.L. and Wikler, K.C. (1988) Development of ganglion cell topography in ferret retina. *J. Neurosci.*, 8: 1194–1205.

Herrmann, K., Antonini, A. and Shatz, C.J. (1994) Ultrastructural evidence for synaptic interactions between thalamocortical axons and subplate neurons. *Eur. J. Neurosci.*, 6: 1729–1742.

Hollander, H. and Vanegas, H. (1977) The projection from the lateral geniculate nucleus onto the visual cortex in the cat. A quantitative study with horseradish-peroxidase. *J. Comp. Neurol.*, 173: 519–536.

Hutchins, J.B. and Casagrande, V.A. (1990) Development of the lateral geniculate nucleus: interactions between retinal afferent, cytoarchitectonic and glial cell process lamination in ferrets and tree shrews. *J. Comp. Neurol.*, 298: 113–128.

Jackson, C.A., Peduzzi, J.D. and Hickey, T.L. (1989) Visual cortex development in the ferret. I. Genesis and migration of visual cortical neurons. *J. Neurosci.*, 9: 1242–1253.

Jhaveri, S., Edwards, M.A. and Schneider, G.E. (1991) Initial stages of retinofugal axon development in the hamster: evidence for two distinct modes of growth. *Exp. Brain Res.*, 87: 371–382.

Johnson, J.K. and Casagrande, V.A. (1991) Transcellular diffusion events of the carbocyanine dye, DiA, in the em-

bryonic ferret visual system. *Soc. Neurosci. Abstr.*, 17: 1133.

Johnson, J.K. and Casagrande, V.A. (1993) Prenatal development of axon outgrowth and connectivity in the ferret visual system. *Visual Neurosci.*, 10: 117–130.

Kirkwood, A. and Bear, M.F. (1994) Hebbian synapses in visual cortex. *J. Neurosci.*, 14: 1634–1645.

Kramer, H. and Cagan, R.L. (1994) Determination of photoreceptor cell fate in the Drosophila retina. *Curr. Opin. Neurobiol.*, 4: 14–20.

Lemmon, V., Farr, K.L. and Lagenaur, C. (1989) L1-mediated axon outgrowth occurs via a homophilic binding mechanism. *Neuron*, 2: 1597–1603.

Linden, D.C., Guillery, R.W. and Cucchiaro, J. (1981) The dorsal lateral geniculate nucleus of the normal ferret and its postnatal development. *J. Comp. Neurol.*, 203: 189–211.

Marcus, R.C., Blazeski, R., Godement, P. and Mason, C.A. (1995) Retinal axon divergence in the optic chiasm: uncrossed axons diverge from crossed axons within a midline glial specialization. *J. Neurosci.*, 15: 3716–3729.

Mavity-Hudson, J., Witty, J.J. and Casagrande, V.A. (1991) The expression of 3-fucosyl-n-acetyl-lactosamine (FAL) epitope in developing interlaminar zones of the tree shrew dorsal lateral geniculate nucleus. *Invest. Ophthal. Visual Sci.*, 32: 1035.

McConnell, S.K., Ghosh, A. and Shatz, C.J. (1989) Subplate neurons pioneer the first axon pathway from the cerebral cortex. *Science*, 245: 978–982.

McKanna, J.A. (1992) Optic chiasm and infundibular decussation sites in the developing rat diencephalon are defined by glial raphes expressing p35 (lipocortin 1, annexin I). *Dev. Dyn.*, 195: 75–86.

Meissirel, C., Dehay, C. and Kennedy, H. (1993) Transient cortical pathways in the pyramidal tract of the neonatal ferret. *J. Comp. Neurol.*, 338: 193–213.

Mitrofanis, J. (1994a) Development of the thalamic reticular nucleus in ferrets with special reference to the perigeniculate and perireticular cell groups. *Eur. J. Neurosci.*, 6: 253–263.

Mitrofanis, J. (1994b) Development of the pathway from the reticular and perireticular nuclei to the thalamus in ferrets: a diI study. *Eur. J. Neurosci.*, 6: 1864–1882.

Mitrofanis, J. and Guillery, R.W. (1993) New views of the thalamic reticular nucleus in the adult and the developing brain. *Trends Neurosci.*, 16: 240–245.

Mooney, R., Madison, D.V. and Shatz, C.J. (1993) Enhancement of transmission at the developing retinogeniculate synapse. *Neuron*, 10: 815–825.

Norris, C.R. and Kalil, K. (1991) Guidance of callosal axons by radial glia in the developing cerebral cortex. *J. Neurosci.*, 11: 3481–3492.

Obermayer, K., Sejnowski, T. and Blasdel, G.G. (1995) Neural pattern formation via a competitive Hebbian mechanism. *Behav. Brain Res.*, 66: 161–167.

Peduzzi, J.D. (1989) Neurogenesis of the geniculate nucleus in the ferret. *Soc. Neurosci. Abstr.*, 15: 1210.

Rakic, P. (1977) Genesis of the dorsal lateral geniculate nucleus in the rhesus monkey: site and time of origin, kinetics of proliferation, routes of migration and pattern of distribution of neurons. *J. Comp. Neurol.*, 176: 23–52.

Ramcharan, E.J., Adams, N.C. and Guillery, R.W. (1995) A study of specialized membrane contacts in the developing rat perireticular nucleus (PRN). *Soc. Neurosci. Abstr.*, 21: 798.

Reese, B.E., Thompson, W.F. and Peduzzi, J.D. (1994) Birthdates of neurons in the retinal ganglion cell layer of the ferret. *J. Comp. Neurol.*, 341: 464–475.

Reh, T.A. and Kljavin, I.J. (1989) Age of differentiation determines rat retinal germinal cell phenotype: induction of differentiation by dissociation. *J. Neurosci.*, 9: 4179–4189.

Robson, J.A. and Geisert, Jr., E.E., (1994) Expression of a keratin sulfate proteoglycan during development of the dorsal lateral geniculate nucleus in the ferret. *J. Comp. Neurol.*, 340: 349–360.

Rockland, K.S. (1985) Anatomical organization of primary visual cortex (area 17) in the ferret. *J. Comp. Neurol.*, 241: 225–236.

Shatz, C.J. and Stryker, M.P. (1988) Prenatal tetrodotoxin infusion blocks segregation of retinogeniculate afferents. *Science*, 242: 87–89.

Shatz, C.J., Chun, J.J.M. and Luskin, M.B. (1988) The role of the subplate in the development of the mammalian telencephalon. In: A. Peters and E.G. Jones (Eds.), *Cerebral Cortex*, Vol. 7. Plenum, New York, pp. 35–58.

Shatz, C.J., Ghosh, A., McConnell, S.K., Allendoerfer, K.L., Friauf, E. and Antonini, A. (1990) Pioneer neurons and target selection in cerebral cortical development. *Cold Spring Harbour Symp. Quant. Biol.*, 55: 469–480.

Smetters, D.K., Hahm, J. and Sur, M. (1994) An N-methyl-D-aspartate receptor antagonist does not prevent eye-specific segregation in the ferret retinogeniculate pathway. *Brain Res.*, 658: 168–178.

Sretavan, D.W. and Shatz, C.J. (1986) Prenatal development of retinal ganglion cell axons: segregation into eye-specific layers within the cat's lateral geniculate nucleus. *J. Neurosci.*, 6: 234–251.

Sretavan, D.W., Pure, E., Siegel, M.W. and Reichardt, L.F. (1995) Disruption of retinal axon ingrowth by ablation of embryonic mouse optic chiasm neurons. *Science*, 269: 98–101.

Stitt, T.N., Gasser, U.E. and Hatten, M.E. (1991) Molecular mechanisms of glial-guided neuronal migration. [Review]. *Ann. N. Y. Acad. Sci.*, 633: 113–121.

Stryker, M.P. and Harris, W.A. (1986) Binocular impulse blockade prevents formation of ocular dominance columns in the cat's visual cortex. *J. Neurosci.*, 6: 2117–2133.

Stryker, M.P. and Zahs, K.R. (1983) On and off sublaminae in the lateral geniculate nucleus of the ferret. *J. Neurosci.*, 3: 1943–1951.

Taylor, J.S.H. and Guillery, R.W. (1994) Effect of a very early monocular enucleation upon the development of the uncrossed retinofugal pathway in ferrets. *J. Comp. Neurol.*, 355: 331–340.

Vitek, D.J., Schall, J.D. and Leventhal, A.G. (1985) Morphology, central projections and dendritic field orientation of retinal ganglion cells in the ferret. *J. Comp. Neurol.*, 241: 1–11.

Wiesel, T.N. and Hubel, D.H. (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophys.*, 26: 1003–1017.

Wilson, J.R., Webb, S.V. and Sherman, S.M. (1977) Conditions for dominance of one eye during competitive development of central connections in visually deprived cats. *Brain Res.*, 136: 277–287.

Wizenmann, A., Thanos, S., von Boxberg, Y. and Bonhoeffer, F. (1993) Differential reaction of crossing and non-crossing rat retinal axons on cell membrane preparations from the chiasm midline: an in vitro study. *Development*, 117: 725–735.