Chapter 2

Development of the retinogeniculate pathway

This chapter summarises the relevant biological data about the development of the retinogeniculate pathway. It is composed of two main sections. The first section introduces the retinogeniculate pathway, describing its main components and how they function. Since cross-species comparisons are difficult, most of the data is taken either from the cat or ferret, since they share similar developmental timetables. The purpose of the first half of this chapter is to introduce the relevant concepts of the early visual pathway. The second half of the chapter, beginning with Section 2.5, considers the role of both activity-independent and activity-dependent processes in the development of the visual system in general and then the retinogeniculate pathway in particular.

2.1 The mammalian visual pathway

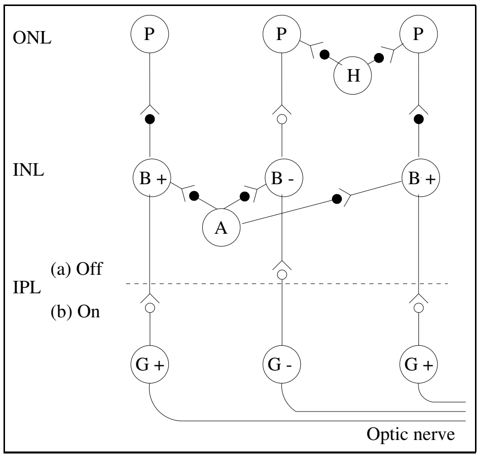
The visual pathway in mammals is composed of around 30 or so different visual areas, each contributing to a different aspect of visual function (Felleman & Van Essen, 1991). The starting point of the mammalian visual pathway is the retina, which converts light into electrical signals. These signals are then passed out of the retina and into two different regions: the LGN and the superior colliculus (SC) (a structure homologous to the optic tectum in other animals). The LGN is located in the thalamus, whereas the SC is located in the midbrain. The LGN and the SC send the processed retinal signals to different regions. Retinal signals to the LGN are destined mainly for cortical areas, whereas signals to the SC are destined for the midbrain. The role of these two different pathways in visual processing is not clear, although it is thought that the cortical pathway is concerned with detailed spatial vision whereas the sub-cortical pathway handles processes of attention and visually guided behaviour.

Although the visual pathway is not strictly hierarchical (Felleman & Van Essen, 1991), there is a progression of complexity of cell responses in the visual areas. In the early parts of the pathway, such as the retina and the LGN, cells have relatively simple receptive field properties, such as the centre-surround response (where cells fire maximally to a light spot on a dark background). In the primary visual cortex (the major recipient of geniculate axons) the cells are much more selective, showing highly tuned responses to stimuli of certain orientations or disparity and wavelength. Higher up in the cortical visual pathway, the complexity of cell response selectivity keeps increasing. For example, around 10% of cells in area IT of the monkey respond maximally to images of either monkey or human faces rather than other stimuli (Perrett, Rolls, & Caan, 1982). In this view, each level of the visual pathway produces receptive field properties that are elaborated on by other areas.

Given the vast size and complexity of the mammalian visual pathway, it is common to study just a small subset of the pathway. The emphasis in this thesis is on retinogeniculate development, and so the next sections will mainly discuss the pathway from the retina to the LGN and up to the cortex. Later in this chapter however, some reference will be made to the sub-cortical pathways, especially the retinotectal pathway.

2.2 The retina

The retina is the starting point of the visual pathway. The retina is a multilayered structure, with both vertical and horizontal pathways connecting together five basic types of retinal cell, as shown in Figure 2.1. Light enters the eye and hits the photoreceptors, where the light is converted into electrical activity. This activity is propagated down (and across) the layers of cells to the final layer of cells, the retinal ganglion cells (RGCs). The RGC axons are then bundled together to form the optic nerve, which carries the visual information into the brain.



Terms	
ONL	Outer nuclear layer
INL	Inner nuclear layer
IPL	Inner plexiform layer
P	Photoreceptor (rod or cone)
H	Horizontal cell
B	Bipolar cell
A	Amacrine cell
G	Ganglion cell
$+$	On-centre cell
$-$	Off-centre cell
$\circ$	Excitatory synapse
$\bullet$	Inhibitory synapse

Figure 2.1: The structure of the retina. The retina contains both a vertical pathway (photoreceptors to bipolars to ganglions) and two horizontal pathways (the horizontal cells and the amacrine cells). This diagram does not show all synaptic interactions nor the large degree of convergence of photoreceptors onto bipolars or bipolar cells onto ganglion cells. Figure adapted from Dowling (1987, p118).

2.2.1 Formation of RGC receptive fields

All photoreceptors hyperpolarise (become more negative) in response to visual stimulation. Photoreceptors then converge onto a bipolar cell by either excitatory or inhibitory synapses. If the synapses are all excitatory, then the bipolar cell also hyperpolarises in response to visual stimulation of the photoreceptors. On the other hand, if the synapses are all inhibitory, the bipolar cell will depolarise (become less negative). As well as inputs from photoreceptors, bipolar cells also receive antagonistic input from horizontal cells, which normally receive synapses from photoreceptors over a wider area.

This combination of direct input from a narrow range of photoreceptors and antagonistic indirect input from a wider range of photoreceptors produces a centre-surround type receptive field profile for the bipolar cells. A bipolar cell with inhibitory input from central photoreceptors is called an on-centre cell since it depolarises in response to stimulation of the central photoreceptors and hyperpolarises in response to stimulation of more peripheral photoreceptors. By similar reasoning, bipolar cells that receive excitatory inputs from central photoreceptors are called off-centre. This convergence of photoreceptors onto bipolars is very high, since over 90% of retinal cells are photoreceptors (Masland, 1996).

The retinal ganglion cells receive their input from two sources: bipolar and amacrine cells. Typically, ganglion cells receive input from a pair of bipolars in a push-pull manner: excitation from one bipolar coincides with removal of inhibition from another bipolar. In this way, ganglion cells are classified as on- or off-centre, according to the centre signs of the excitatory bipolar. The sign of the ganglion cell can also be determined morphologically by examining the dendritic branching point of the ganglion cell: dendrites stratifying in sublamina A of the IPL are off-centre, whereas those dendrites stratifying in sublamina B belong to on-centre ganglion cells. (Nelson, Famiglietti, & Kolb, 1978). The additional input to ganglions from amacrine inputs work in an antagonistic manner, similar to horizontal cells, although the function of amacrine cells is not clear.

As well as classification of RGCs into on- or off-centre, according to the sign of the receptive field, RGCs are further divided into three main categories according to both physiological and anatomical criteria (Stone, 1978, 1983). X cells have medium-sized cell bodies, and comprise around 40% of the ganglion cell population. Y cells have large-sized cell bodies, but make up less than 10% of the number of ganglion cells. The remaining 50% or so of cells have a range of cell-sizes and physiological properties, and are classed as W cells. The different classes of RGC have different responses to the same visual stimuli, meaning that the stimuli are processed in different ways. For example, X cells have a sustained response to stimuli which is useful for fine-detailed spatial processing, whereas Y cells have more transient responses making them much more suitable for motion analysis. The W class of cells is a heterogeneous class, and although the percentage of W cells in cats and ferrets is quite high, comparatively little is known about them since they project mainly to sub-cortical rather than cortical structures.

The retina does not uniformly sample the visual world. The central part of the visual field is sampled at a much higher density than peripheral parts of the visual field. Additionally, the size of receptive fields of retinal cells varies with the eccentricity of the cell — cells in the fovea have small receptive fields, whereas cells in the periphery have large receptive fields.

2.3 The LGN

The LGN is the primary recipient of retinal axons. The pathway from the retina to the LGN is illustrated in Figure 2.2. The optic nerve from each eye meets at the optic chiasm, at which point axons from the nasal part of the retina cross over to the other side of the brain, whereas axons from the temporal retina remain on the same side. (It is thought that molecular markers are responsible for causing the temporal retinal axons to stay on the same side of the brain, whereas the nasal retinal axons cross over to the other side (Wingate & Thompson, 1995).) The axons leave the optic chiasm to form an optic tract on each side of the brain to innervate the appropriate LGN. In this way, each LGN receives inputs from areas of the two retinae which correspond to the same part of the visual field.

For most animals, the size of the inputs to the LGN from the two retinae are different: the contralateral retinal input (that coming from the retina on the opposite side of the brain to the LGN) is larger than the ipsilateral (same side) input. The difference in size of the contralateral and ipsilateral input is related to the positioning of the animal's eyes on its head, and so varies from species to species. In animals with laterally placed eyes, such as the grey squirrel, the size of the monocular input is very large. In comparison, animals with forward placed eyes (such as cats and monkeys) tend to have a large binocular field and hence the contralateral and ipsilateral inputs are more balanced (Kaas, Guillery, & Allman, 1972), although the contralateral input is still larger than the ipsilateral input.

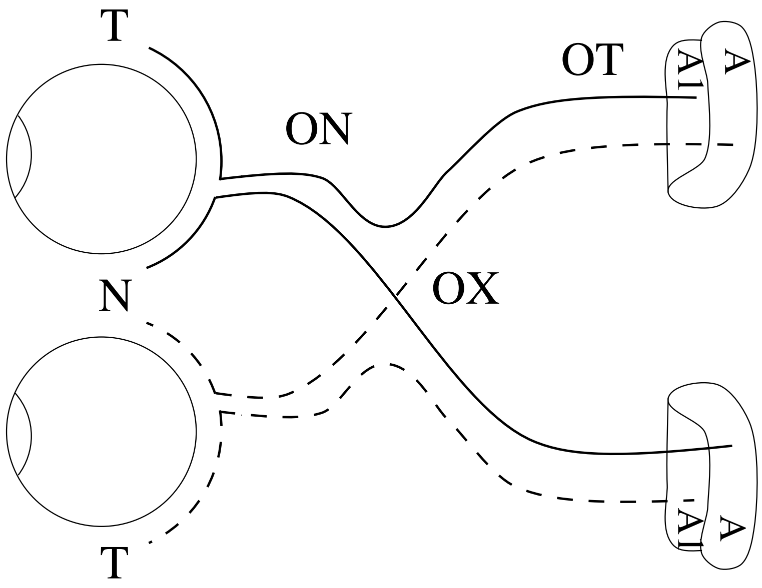


Figure 2.2: The visual pathway from the retina to the geniculate. Key: T – temporal retina. N – nasal retina. ON – optic nerve. OX – optic chiasm. OT – optic tract. A – LGN layer A. A1 – LGN layer A1.

2.3.1 LGN cell types

There are two classes of cells found in the geniculate: relay cells and interneurons. Approximately 75% of LGN cells are relay cells, the other 25% are inhibitory interneurons (LeVay & Ferster, 1979). The relay cells receive excitatory input from between one and five retinal cells (Cleland & Dubin, 1971, 1976). Relay cell axons leave the LGN to form the geniculocortical pathway, connecting the LGN to layer IV of area 17 of the cortex. The interneurons only make local inhibitory connections within the geniculate and do not project to other areas.

Relay cells can be classified into several subtypes. First, they can be labelled on- or off-centre, depending on their centre-surround response to light. Second, they can also be classified as X- or

Y-like, depending on whether they show a null-response to sinusoidal gratings, as an analogue of the retinal X and Y classes (Bowling & Wieniawa-Nakiewicz, 1986).

2.3.2 Receptive fields of LGN relay cells

The spatial receptive field profiles of relay cells are similar to RGCs, although the inhibitory surround region tends to be stronger (Hubel & Wiesel, 1961), probably due to the effect of the inhibitory geniculate interneurons. This similarity of receptive fields is due to the low convergence of RGCs onto relay cells: typically a geniculate cell receives its inputs from between 1–5 retinal cells which tend to be from the same eye and of the same polarity (on- or off-centre) (Mastronarde, 1987a).

This similarity of retinal and geniculate spatial receptive fields has led to the notion of the geniculate as a "relay station", transferring retinal information without significant processing to the cortex. For example, geniculate cells show a slight orientation selectivity, but this property originates in the retina, and is formed by the oriented dendritic fields of retinal cells rather than being generated in the retinogeniculate pathway (Levick & Thibos, 1982; Leventhal & Schall, 1983). Similarly, the direction-selectivity found in some geniculate cells (Thompson, Zhou, & Leventhal, 1994) is most likely a reflection of the sensitivity of their retinal inputs (Shou, Leventhal, Thompson, & Zhou, 1995).

In the temporal domain however, geniculate cell responses differ quite strongly from retinal cells. Around two-thirds of geniculate cells exhibit a lagged response to retinal stimuli (Mastronarde, 1987a, 1987b). This temporal distinction has led to geniculate cells being further categorised as either lagged or non-lagged (Humphrey & Weller, 1988). Although the function of this lagged response is not clear, it could be used to generate various cortical responses such as direction selectivity (Saul & Humphrey, 1990).

Finally, X and Y relay cells can fire in one of two modes: tonic or bursting (Guido, Lu, & Sherman, 1992; Sherman & Guillery, 1996). In tonic firing, the cell responds with multiple action potentials that correspond in a linear fashion to the stimuli. In comparison, in burst mode the response to the stimulus is highly non-linear, comprising of one or two action potentials to stimulus onset and then no further action potentials for the rest of the stimulus presentation. It is thought that the two modes are suitable for different functions. Bursting mode is better suited for the initial detection of stimuli as a way of directing attention to a particular stimulus. Tonic mode however is more suited for faithful transmission of the retinal signal.

The subject of this thesis is the neural pathway from the retina to the LGN, which is commonly termed the retinogeniculate pathway. In particular, this thesis is concerned with the development of topography and ocular segregation in this pathway. These two properties will now be discussed in more detail.

2.3.3 The retinotopic mapping in the LGN

When the optic tract reaches the LGN, the axons innervate the LGN in such a way that neighbouring retinal cells tend to project to neighbouring geniculate cells. This is known as a retinotopic or topographic mapping. Such maps are commonly found not only within visual areas, such as area 17, but also in other sensory areas such as the somatosensory cortex (Kaas, Nelson, Sur, &

Lin, 1979). However, the projection of retinal space into the geniculate is not just a conventional topographic mapping. Most maps project an input space into an output space of either the same or lower dimensionality. In the LGN however, the dimensionality of the spaces is reversed: although the retina is regarded as a two-dimensional sheet of cells, the LGN is a three-dimensional block of cells. The mapping is organised such that a point of visual space in the retina projects to a column of cells within the LGN. This group of LGN cells is termed a ‘projection column’, which is normally defined as a column of LGN cells which contains 90% of all cells with receptive fields (RFs) responding to the same region of visual space (Sanderson, 1971b). Typically, these columns are oriented perpendicular to the LGN layers.

Although cells within a projection column receive input from the same region of visual space, they can respond in different ways to the same stimulus. For example, X relay cells at different depths within a column respond to the same stimuli with different timing latencies. These latencies could be useful for creating certain selectivities of cortical cells, such as direction selectivity (Bowling, 1989a).

The mapping of retinal space into the cat LGN is shown in Figure 2.3. The layout of retinal space in the ferret follows similar retinotopic principles, although the ferret LGN is positioned differently (Zahs & Stryker, 1985). Just as the retina has more cells representing the central visual field, so does the LGN, as can be seen from the amount of geniculate covering the central $\pm 2°$ in comparison with the amount covering 10–20°. However, equal numbers of RGCs project to equal volumes in the LGN, and so the gradient of visual field representation in the geniculate is a reflection of RGC density gradient (Sanderson, 1971b).

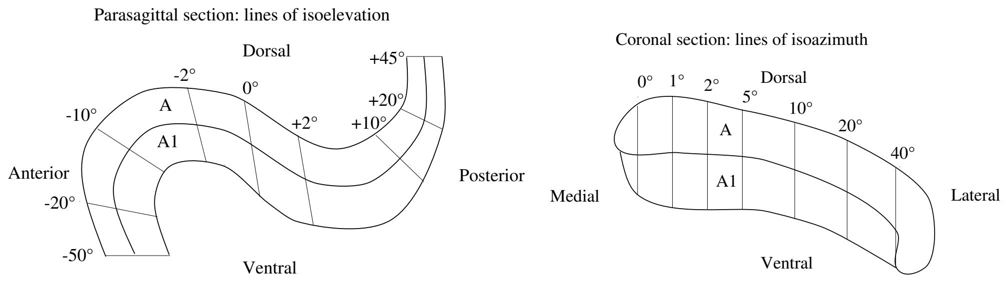


Figure 2.3: The topography and layering of the cat LGN — parasaggital and coronal views. Parasagittal view adapted from Figure 9 of (Sanderson, 1971a). Coronal view adapted from Figure 14 of (Sanderson, 1971a). The C layers have been omitted here for clarity, but lie just below layer A1. The region of layer A to the right of the 40° isoazimuth line is known as the monocular segment, since there is no corresponding region for layer A1. As can be seen from the lines of isoazimuth and isoelevation, the central visual field is overrepresented in the LGN. These lines of isoelevation and isoazimuth can be regarded as projection columns.

2.3.4 Ocular segregation in the LGN

Both the cat and ferret LGN are divided into three layers — A, A1 and C. (The C layer is commonly divided further into sublayers — C, C1, C2 and C3. When considering the retinogeniculate pathway the C laminae are normally ignored, since it mainly receives input from W ganglion cells and mostly projects onto subcortical structures.) These layers are defined according to several criteria, including its cytoarchitecture (the grouping of cells into cell-rich strata and cell-poor spaces, and their size distribution), the morphology of individual cells, and by the segregation of the retinal inputs (Casagrande & Brunso-Bechtold, 1985). In this thesis, we are mainly concerned with this last criteria, the segregation of retinal inputs: in the mature LGN, contralateral inputs innervate layer A, whereas ipsilateral inputs innervate layer A1. Details of the segregation of retinal inputs according to eye of origin and class are given in Table 2.1.

LGN layer	Eye of input	Class of retinal cell
A	Contra	X/Y
A1	Ipsi	X/Y
C	Contra	Y
C1	Ipsi	W
C2	Contra	W
C3	Non-retinal	—

Table 2.1: Class of retinal input to each layer of the cat LGN, showing the eye of origin of retinal inputs and physiological class of retinal input (Sherman, 1985). There are no retinal inputs to layer C3 — inputs to this layer come from midbrain structures.

2.3.5 Sublayering in the LGN

Within a geniculate layer, there is evidence for further segregation of retinal inputs according to the class of retinal cell. The strongest form of sublayering is the segregation of on- and off-centre relay cells. In the ferret, both layers A and A1 divide into on and off leaflets (Stryker & Zahs, 1983), as shown in Figure 2.4. In the cat, the sublayering is not so strict, showing more of a tendency for on-centre cells to be found dorsally within a layer and off-centre cells to be found ventrally (Bowling & Caverhill, 1989; Thurlow, Bowling, & Cooper, 1993). It has also been proposed that the on- and off-centre cells are organised into columns perpendicular to the layers (Berman, Naporn, & Payne, 1987; Berman & Payne, 1989). Later studies however could not verify such an organisation, suggesting that the initial results were a product of the multi-unit recording technique (Bowling & Caverhill, 1989).

As well as cells clustering according to centre sign, X and Y RGCs also tend to arborise differently in the cat, with around 60% of X cell boutons clustering at the top of a layer, and about 70% of Y cell boutons clustering in the lower half of a layer (Bowling & Michael, 1984) — although see Sur, Esguerra, Garraghty, Kritzer, and Sherman (1987) for some qualifications. This clustering of boutons produces a slightly unexpected organisation of geniculate cells: geniculate Y-like cells tend to be found at the borders of the layers, with X-like cells more concentrated in the centre of the layers (Bowling & Wieniawa-Nakiewicz, 1986). Finally, there is also a tendency for relay cells with similar orientation preference to be clustered together (Shou & Leventhal, 1989). This does not produce any sublayering however, since the orientation preference of neighbouring cells varies smoothly throughout the depth (both perpendicularly and obliquely) of the LGN.

2.4 The functions of the LGN

Given that the spatial receptive field profiles of geniculate cells are fairly similar to their retinal inputs, it is commonly assumed that the LGN is merely a relay station sending its retinal inputs

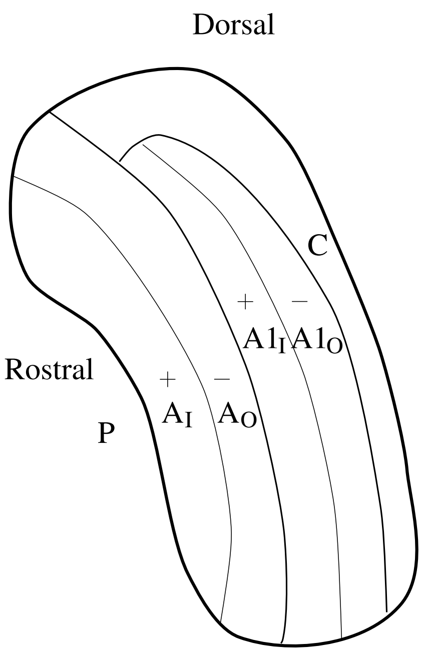


Figure 2.4: The sublayering of on- and off-centre cells in the ferret LGN. The figure shows a parasaggital view of the LGN. Inner leaflets of a layer are indicated with an I subscript and outer leaflets with an O subscript. The polarity of cells within the leaflets are indicated by + (on-centre) and – (off-centre). The P indicates the location of the perigeniculate nucleus (PGN). Figure adapted from (Stryker & Zahs, 1983).

onto cortical areas without significant processing. In this thesis, the focus is placed on the way the retinogeniculate mapping develops, rather than on the role of the LGN in visual processing. It is worth briefly reviewing however some of the possible roles that the LGN may play in the processing of visual information.

2.4.1 The corticogeniculate pathway

Although the LGN is the primary recipient of retinal axons, these axons only account for between 10–20% of excitatory input to geniculate relay cells — the most dominant source of input to relay cells is from cells in layer VI of the visual cortex, accounting for around 50% of the input (Sherman & Koch, 1986). (The remaining 30–40% of relay cell input comes from LGN interneurons and perigeniculate cells). Cortical cells also project back onto LGN interneurons, although relay cells receive roughly twice as many synapses from cortical cells as interneurons (Montero, 1991). This projection is topographic, such that cortical cells responding to contralateral (or ipsilateral) input tend to synapse back onto relay cells in layer A (or A1) (Murphy & Sillito, 1996).

This pathway, the corticogeniculate pathway, is often termed a feedback pathway, although the term 'feedback' is slightly misleading due to its large size. In terms of the numbers of axons, it is the biggest geniculate pathway, as shown in Figure 2.5. Given the evolutionary pressure to reduce the amount of wiring in the brain, the LGN must be doing something significant to justify such a large corticogeniculate pathway (Jones, 1985).

The purpose of this pathway is as yet unclear, although it is commonly assumed that it gates the flow of retinal information to the cortical areas in some way. Another common view is that

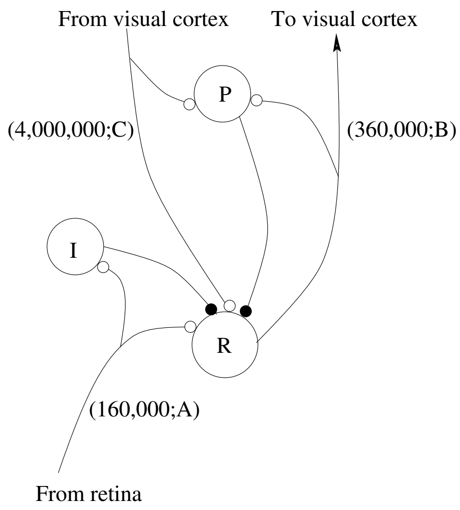


Figure 2.5: Summary of the main inputs to cat LGN X relay cells and their approximate magnitudes. The Y pathway is simpler than the X pathway, since LGN interneurons are not involved. Figure adapted from (Sherman & Koch, 1990). Numbers in parentheses indicate the approximate size of the pathway along with the references: A — (Williams et al., 1986), B — (LeVay & Ferster, 1979), C — (Sherman & Koch, 1986). Excitatory synapses are open, inhibitory synapses are filled. Cell types: R — LGN relay cell, I — LGN interneuron, P — perigeniculate cell.

the LGN is an "internal retina" which, unlike the real retina, can have its activity altered by inputs coming from other (mostly cortical) areas (Singer, 1977). This view has been developed into a general notion that thalamic areas are "active blackboards" for cortical areas to use as places to collect information and update hypotheses (Mumford, 1991). The corticogeniculate pathway has also been suggested to form a crucial role in shaping cortical cell responses such as "end-stopping" (preference for short stimuli rather than long stimuli) (Murphy & Sillito, 1987). Another possibility is that the corticogeniculate pathway acts to synchronize the activity of geniculate relay cells that are responding to a certain stimulus. This in turn helps cortical cells to respond to one particular stimulus since the relay cells are now more likely to be firing coherently, making the stimulus more salient (Sillito, Jones, Gerstein, & West, 1994; Singer, 1994). Finally, cortical inputs to geniculate relay cells can affect the low-threshold Ca^{2+} conductance of the cell and thus switch the cell from a bursting mode to a tonic mode (Sherman & Guillery, 1996), which dramatically affects its response to stimuli.

Regardless of the function of the corticogeniculate pathway, the gating of signals is assumed to be performed by interaction with cells in the reticular nucleus formation (RNT). This lies dorsally and anterior to the thalamus. Axons from each thalamic area, including the LGN, send side-branches out to an appropriate area of the RNT on their way to the cortex. Additionally, cortical axons also make side branches into the RNT on their way back to the appropriate thalamic area. The area of the RNT linked to LGN relay cells is known as the perigeniculate nucleus (Sherman & Koch, 1990), and is illustrated in Figure 2.5.

2.4.2 Other theories of LGN function

The main theories regarding the role of the LGN in visual processing are dominated by the existence of the corticogeniculate pathway and have been outlined above. In this section we briefly consider some of the other theories.

One role of the LGN may be to organise the retinal inputs in a way that can help cortical processing by grouping together certain cells so that they are close together. For example, the segregation of inputs in the LGN is maintained in the projection to the cortex. In the cat, central regions of the A laminae project to layer IVb of cortical area 17, whereas border regions project to layer IVa (Bowling, 1989b).

Alternatively, since there are around four times as many geniculate relay cells than RGCs (Sanderson, 1971b), there is considerable divergence in the retinogeniculate pathway. This divergence could give the cortex a fairer representation of the X and Y cell pathways. In the retina, there are around five times as many X RGCs as Y RGCs. In the geniculate, this ratio is reduced to around 2:1, since Y-RGCs innervate many more LGN relay cells than X RGCs (Sur et al., 1987; Sherman & Koch, 1990). This increase in the proportion of Y-like cells in the geniculate reduces the dominance of the X pathway that exists in the retina.

Another role of the LGN may be captured in the way that geniculate cells respond over time. Lagged and non-lagged geniculate cells can transform retinal responses in the temporal domain. It has been hypothesised that just as the retina removes spatial correlations using centre-surround receptive fields (Atick & Redlich, 1992), the LGN removes temporal correlations using the temporal response characteristics of lagged and non-lagged cells (Dan, Atick, & Reid, 1996). Finally, it has also been suggested that geniculate cells adjust the variance of retinal signals on their way to the cortex, transforming the non-linear variance of retinal cell firing rates to mean firing rates into linear variances. (Levine, Cleland, Mukherjee, & Kaplan, 1996).

2.5 Factors influencing neural development

The first half of this chapter has focused on the properties of the visual pathway from the retina, through the LGN, up to the cortex, and back down to the LGN. The second half of this chapter considers the central question of how this pathway comes into existence during the early stages of the animal's development. In general, we are concerned with how one set of cells, the presynaptic cells, connects to another group of cells, the postsynaptic cells, to produce the mature pattern of ocular segregation and topographic mapping. For the specific problem of retinogeniculate development, the presynaptic cells are the retinal cells, and the postsynaptic cells are the geniculate cells (or tectal cells, depending on the species). In this section we also the consider the development of similar sensory pathways, both visual and non-visual.

2.5.1 Marker theories and genetic specification

The early investigations into the development of visual pathways were commonly performed in amphibians, rather than mammals. Such pathways commonly show no intermixing of signals from different eyes, although the retinotectal mapping is retinotopic, as shown in Figure 2.6.

To look at the development of this retinotectal mapping, experiments by Sperry and colleagues through the 1940–1960s examined the regrowth of retinal cells into the optic tectum in amphibians after the optic nerve had been severed. Their results showed that when retinal ganglion cells grew back into the tectum, they always seemed to know which part of the tectum to innervate. On the basis of this and similar experiments, Sperry proposed the 'chemoaffinity hypothesis' (Sperry, 1963). Applied to the retinotectal pathway, it claims that each retinal cell has a unique marker, and the tectal cell to which the retinal cell should be wired to carries the same unique marker. During development, each retinal cell searches for the tectal cell with the same (or closest) marker and then connects to it.

The chemoaffinity hypothesis assumes that the connectivity of the cells is rigidly determined by the distribution of markers in the retinal axons and in the tectum. However, several mismatch experiments showed that abnormal retinotectal mappings could develop during regrowth. For example, Gaze and Sharma (1970) showed that a whole retina could re-grow onto half a tectum in a topographic fashion, as shown in Figure 2.7. These and other regrowth experiments showed that there is not a fixed affinity between retinal and tectal cells. (A thorough review of the various mismatch experiments, along with a computer model accounting for most of the biological evidence, is given by Willshaw and von der Malsburg (1979), showing that in many cases the regenerated maps are very different to the maps that would be expected from a fixed chemoaffinity process.)

Despite this evidence from regeneration experiments, it is highly likely that chemical markers of some form are used early in pathway development (Goodman & Shatz, 1993), but by themselves they do not account for the full development of the visual system. So, what other processes are crucial in development?

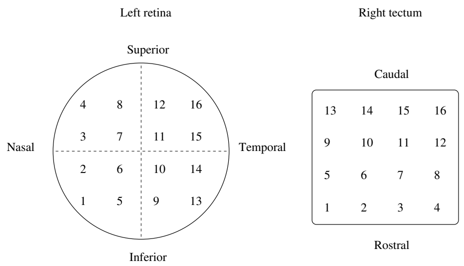


Figure 2.6: The retinotopic mapping of the left retina onto the right optic tectum. Numbered retinal cells normally innervate the appropriately numbered area of the tectum. The topography of the retina is preserved in the tectum, such that neighbouring retinal cells innervate neighbouring areas of the tectum. Figure adapted from (Gaze & Sharma, 1970).

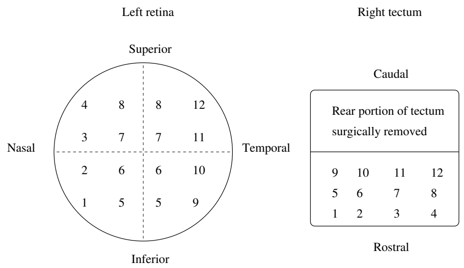


Figure 2.7: The retinotectal mapping following removal of the caudal half of the tectum. The retinal mapping is compressed so that the remaining half of tectum still shows an orderly mapping of retinal space. Although the map in the tectum is still orderly, some tectal cells (marked 5–8) can be stimulated by more than one region of the retina as a result of the compression. Figure adapted from (Gaze & Sharma, 1970).

2.5.2 The role of experience in development

The role that visual experience plays in the development of visual pathways was first assessed by a series of experiments looking at the development of ocular dominance in cat visual cortex (Wiesel & Hubel, 1963a, 1963b; Hubel & Wiesel, 1963). In a newborn kitten, most cortical cells in the primary visual cortex (area 17) respond to stimulation of either eye, although there is a bias favouring stimulation of one of the eyes. After around six weeks of normal visual experience, most cells have adapted to respond to stimulation of only one eye, ignoring stimulation from the other eye. Overall, both eyes normally innervate an equal number of cortical cells. However, if one of the eyes is covered from birth for six weeks so that it does not receive any visual input, most (if not all) of the cortical cells do not respond to stimulation of the eye that was deprived of vision. Wiesel and Hubel (1963a) repeated these experiments with kittens of different ages. They found that the older the kitten was at the onset of deprivation, the weaker the effects of deprivation. Furthermore, depriving one eye of vision during adulthood did not affect the pattern of ocular dominance at all. These results indicated a critical period of development, during which visual deprivation radically alters development, and after which the effects of deprivation are weakened.

Other deprivation experiments examined the effects of visual deprivation on the orientation selectivity of cortical cells. The cortical cells of normal cats have a preference for stimuli of a particular orientation. The distribution of these orientation preferences is complete: taking a population of cells, all possible preferred orientations are found. If a newborn kitten is raised in a restricted visual environment consisting of either horizontal or vertical lines, the effect on the distribution of preferred orientations is severe: most cells developed a preference for either horizontal or vertical lines and cells preferring oblique lines were rare (Hirsch & Spinelli, 1970; Blakemore & Cooper, 1970).

A different approach to studying development has been to reroute visual inputs into non-visual thalamic areas (Sur, Garraghty, & Roe, 1988). Sur and his colleagues rerouted retinal signals of newborn ferrets into the auditory thalamus. The ferrets were then raised to maturity. After maturation, cells in the auditory thalamus were found to be responsive to visual stimulation. Furthermore, cells in the auditory cortex were also found to be responsive to visual stimuli, exhibiting orientation and directional selective receptive field properties. These properties are similar to those found in normal ferret visual cortex, although the receptive fields tended to be broader and more sluggish than normal. Sur et al. conclude by suggesting that "the modality of a sensory thalamic nucleus or cortical area may be specified by its inputs during development". In other words, it could be that there is nothing intrinsically special about the visual cortex: it becomes the main area for visual processing just because it receives visual input.

Similar experiments have since been performed in other animals. Métin and Frost (1989) rerouted newborn hamster visual inputs into somatosensory cortex and then reared the hamsters to adulthood. They found that somatosensory cells developed visual receptive field properties similar to those found in normal hamsters. A slightly different approach was taken by Schlaggar and O'Leary (1991), transplanting a section of embryonic rat occipital cortex (normally the area which develops to become the visual cortex) to somatosensory cortex. Normal somatosensory cortex develops "barrels", which are not found elsewhere in the cortex. In the transplanted occipital cortex however, barrels similar in shape and distribution to normal somatosensory barrels were found. Hence the ability to generate barrels is not due to some intrinsic property of somatosensory cortex, but instead could be generated by the thalamic inputs to cortex.

Taken together, there is a wide range of evidence showing that development of visual pathways does not just follow a strict genetic blueprint: visual experience also plays an important role. A popular principle based on the results from the experiments just outlined is that the cortex makes use of activity-driven processes — processes that are driven by the neural activity in the visual pathway (Goodman & Shatz, 1993). Quite often, these processes are self organising, in that the neurons adapt according to the pattern of activity in the system, rather than developing according to some predefined program (von der Malsburg & Singer, 1988). For example, Blakemore and Cooper (1970) hypothesised that:

> the visual cortex may adjust itself during maturation to the nature of its visual experience. Cells may even change their preferred orientation towards that of the commonest type of stimulus; so perhaps the nervous system adapts to match the probability of occurrence of features in its visual input. (Blakemore & Cooper, 1970, p478)

In this framework, the deprivation experiments alter cortical cell responses by altering the statistics of the visual environment, and therefore the levels and patterns of neural activity in the system. The results of the re-routing and transplant experiments can also be explained using an activity-dependent process: each part of the cortex adapts via general modification principles to its inputs, regardless of the sensory modality of the inputs.

2.6 Development of the LGN

Are activity-driven processes responsible for any development of the LGN? The previous section has shown that many aspects of postnatal development of the visual system rely on activity-dependent processes, with the neural activity being generated by visual stimulation of the retina. However, in the case of the ferret and cat LGN, the development of ocular segregation and topography has begun before eye opening. This rules out any processes driven by visually-evoked neural activity. This section considers the development of the LGN before the onset of visual stimulation and considers if activity-driven processes are responsible for any aspects of LGN development.

2.6.1 Normal development

The normal sequence of development for the cat and ferret retinogeniculate pathway are summarised in Tables 2.2 and 2.3. The cat and ferret share a common sequence of neural development, although the ferret is born about three weeks earlier than the cat. Most developmental experiments are therefore performed on the ferret postnatally rather than in the cat prenatally since it is easier to perform the experiments in postnatal animals.

The sequence of normal development in the cat

In the cat, retinal axons begin to enter the LGN at around embryonic day 32 (E32). The contralateral eye has a competitive advantage because its axons innervates the LGN around three days before axons from the ipsilateral eye (Shatz, 1983). When an retinal axon innervates the LGN, it tends to give off side-branches throughout both layers A and A1 of the LGN, so that most regions

Day	Event
E23	Retinal axons are yet to arrive at the optic chiasm (Sherman, 1985).
E30–E40	Correlated bursting activity begins (R. Wong 1994, personal communication).
E32	First retinal axons reach the LGN. During next two weeks, most cells in A and A1 remain binocular (Sherman, 1985).
E38	Functional synaptic transmission exists between ganglion cell axon and LGN neuron (Shatz, 1994).
E47	Segregation of retinal inputs into laminae begins.
E48	Loss of ganglion cells begins (Sherman, 1985).
E60	Retinal OPL appears (Greiner & Weidman, 1980).
E63	Birth.
P5	RGC dendrites begin to unistratify into one of the two IPL sublayers of the retina (Maslim & Stone, 1988).
P6	Rod photoreceptors still developing (Sidman & Wislocki, 1954).
P10	Eye opening (Greiner & Weidman, 1980).

Table 2.2: Timescale of cat retinogeniculate development. Days are given as either embryonic (E) or postnatal (P).

of the LGN initially receive input from both eyes (although some regions are solely innervated by contralateral axons throughout development).

By E48, the segregation into eye-specific layers has begun. The majority of axons from the contralateral eye solely innervate layer A, and most of the ipsilateral axons only innervate layer A1. This is achieved by the elimination of inappropriate side-branches and the elaboration of branches in the appropriate layer. Cellular lamination cannot yet be seen at E48, but occurs later at around E62, just before birth (Shatz, 1983). By birth, the LGN has clearly segregated into eye-specific layers. At this stage however, the development of the retinal circuitry is lagging far behind that of the geniculate. The retinal photoreceptors and most of the rest of the retinal circuitry are still developing early after birth (Greiner & Weidman, 1980). Only by around P7–10 do the eyelids open — long after the onset of eye-specific segregation in the geniculate.

The sequence of normal development in the ferret

The normal pattern of development in the ferret is similar to cat development, with the difference that most of the development occurs postnatally. In addition, the segregation of on- and off-centre inputs occurs sometime in the third postnatal week, P14–21 (Linden, Guillery, & Cucchiaro, 1981). Shortly before this time, the RGCs dendrites restrict themselves to the appropriate sublayer in the IPL of the retina (P9, Wingate & Thompson, 1995).

2.7 Neural activity in the developing retina

Activity-dependent processes require neural activity in order to work — is there any such activity present at the time when the LGN is developing? In the case of LGN development, any activity

Day	Event
E28	Retinal axons have not yet innervated LGN (Guillery, Lamantia, Robson, & Huang, 1985).
E41	Birth.
	Contralateral axons are extended further into the LGN than ipsilateral axons (Linden et al., 1981).
P4–7	Eye specific layers form (Linden et al., 1981).
P9	On- and off-centre RGCs restricted within the IPL (Wingate & Thompson, 1995). On- and off-centre RGCs fire synchronously (Wong & Oakley, 1996).
P14–21	Axon terminals segregate into on and off sublayers in LGN (Linden et al., 1981; Hahm, Langda, & Sur, 1991).
P17	Asynchronous firing of on- and off-centre RGCs present (Wong & Oakley, 1996).
P30	Waves are no longer present (Wong et al., 1993).
	Eyes open (same time as cat in terms of days post-conception) (Linden et al., 1981; Wingate & Thompson, 1995).

Table 2.3: Timescale of ferret retinogeniculate development. Days are given as either embryonic (E) or postnatal (P).

cannot be the result of visual stimulation for two reasons. First, the eyes are not open in the cat until around P7–10 (Greiner & Weidman, 1980), by which time the LGN has considerably developed. Second, the retinal circuitry is still developing and the photoreceptors are not yet mature (Sidman & Wislocki, 1954; Greiner & Weidman, 1980). It is therefore highly unlikely that any activity in the retina can be generated by visual stimulation. Is there any retinal activity in the absence of visual stimulation?

Since the early 1980's, it has been known that retinal ganglion cells in the adult cat have a significant maintained discharge even in the absence of visual stimulation. Furthermore, neighbouring retinal ganglion cells show correlated activity patterns, whereas more distant pairs of cells do not. Finally, the correlation respects the polarity of the cells: neighbouring like-centred pairs of cells are correlated, whereas neighbouring opposite-centred pairs of cells are anticorrelated (Mastronarde, 1983a, 1983b, 1983c). However, such measurements were only performed on adult cats, leaving open the question of whether such correlations are present in developing animals.

2.7.1 Waves of spontaneous activity

The possibility of correlated retinal activity before the onset of patterned vision has recently been addressed by a set of experiments recording from the developing retina. The existence of neural activity in the developing retina was first reported by Galli and Maffei (1988). In vivo recordings of rat retinal ganglion cells aged E17–E21 showed individual cells were spontaneously active. (The term *spontaneous* was used to emphasise that the activity was not evoked by visual or other external stimulation.) Further studies in the prenatal rat using pairs of electrodes to record from two or three neighbouring ganglion cells showed that neighbouring ganglion cells are correlated in their activity patterns: they tend to fire together, and be silent together (Maffei & Galli, 1990).

These experiments confirmed the existence of spontaneous activity, correlated across neighbouring retinal cells, in the developing retina.

Since then, two developments in recording techniques have revealed more details about the nature of this spontaneous activity. First, the development of the multielectrode array has allowed the activity of around one hundred neighbouring retinal ganglion cells to be recorded simultaneously (Meister et al., 1991). These recordings show that the cells fire synchronously, producing waves of activity that move across the retina. Typically, these waves last for a few seconds, and then the patch of retina being recorded is quiet for around a minute before another wave begins. As the retina develops, the waves tend to be present for longer and are broader. By P30, the waves are no longer detectable and have been replaced by normal adult maintained activity levels (Mastronarde, 1983a; Wong et al., 1993).

Second, the use of fluorescent dyes in optical imaging have revealed fluctuations in levels of intracellular calcium in the retinal ganglion cell layer (Wong, Chernjavsky, Smith, & Shatz, 1995). This imaging technique has allowed the mechanisms generating the waves to be investigated in more detail, suggesting that the horizontal pathway in the retina (amacrine–ganglion) is responsible for generating the waves, rather than the vertical pathway (photoreceptors–bipolar–ganglion). This optical imaging technique has also been used to demonstrate that the correlations between on- and off-centre retinal cells changes over time. In the ferret, neighbouring on- and off-centre ganglion cells have similar firing patterns for the first two weeks of postnatal life. However, at around P17, the firing patterns of on- and off-centre cells differs: off-centre cells tend to fire much more often than on-centre cells, such that when an on-centre cell fires, so does an off-centre cell, but not vice-versa (Wong & Oakley, 1996). This distinct firing pattern occurs at around the same time as when LGN layers are segregating into on- and off-centre leaflets (Hahm et al., 1991).

2.8 The central hypothesis

The existence of correlated activity in the retina during the period of retinogeniculate development has led many people to the hypothesis at the centre of this thesis (Maffei & Galli, 1990; Jeffery, 1989; Meister et al., 1991; Wong et al., 1993):

> The correlated spontaneous activity in the retina drives Hebbian-based synaptic modification processes to develop the patterns of ocular segregation and topography in the retinogeniculate pathway.

Although this hypothesis is specifically concerned with retinogeniculate development, it is also thought to apply to the refinement of other sensory pathways (Wong, 1993; Katz & Shatz, 1996), such as the avian auditory pathway (Lippe, 1994), and rat somatosensory cortex (Yuste, Peinado, & Katz, 1992).

2.8.1 Propagation of retinal waves to the LGN

A pre-condition for the waves to drive retinogeniculate development is that retinal axons must be making functional connections to the geniculate during development. This seems to be the case: cat geniculate cells can be activated by electric stimulation of one or both of the optic nerves from E39 onwards (Shatz & Kirkwood, 1984). More recent work in the neonatal mouse (P0–4) has shown that LGN neurons are driven to generate an action potential (or 'spike'), and that the period of spiking (every 30–90 seconds) matched the period of firing in the retina (Penn et al., 1995; Mooney, Penn, Gallego, & Shatz, 1996). Hence, not only are there functional synapses between the retinal and geniculate cells, but retinal waves can drive geniculate neurons to spike. Furthermore, groups of LGN neurons were correlated in their firing patterns, making it likely that the spontaneous activity may propagate into, and modify, the geniculocortical pathway (Mooney et al., 1996).

2.8.2 Abnormal development of the LGN

Does the LGN develop according to some predefined genetic program, or can its development be influenced by environmental factors? This section describes some of the ways in which LGN development is affected by various conditions, both natural and experimental.

Evidence that the LGN is not purely hard-wired comes from Siamese cats (Shatz, 1977). In these cats, a genetic mutation causes temporal ipsilateral retinogeniculate axons to be misrouted at the optic chiasm. This causes the axons to end in layer A1 of the contralateral LGN, rather than in their normal target, layer A1 of the ipsilateral LGN. (However, it is possible that the genetic mutation also directs the temporal ipsilateral retina to the contralateral geniculate.)

Experimental manipulations to the retinogeniculate pathway also affects its development. In the ferret, for example, the removal of both eyes before the retinal axons reach the LGN (E28) prevents development of the eye-specific laminae (Guillery et al., 1985). When one eye is removed from the ferret at birth, the remaining eye innervates its normal region, as well as some other geniculate regions which are normally innervated by the eye which has been removed. For example, in the LGN ipsilateral to the surviving eye, layer A1 is thicker than normal and includes part of the nucleus that is normally the monocular segment (Guillery et al., 1985). Furthermore, when one eye in the ferret is removed at P0, the remaining eye innervates the whole of both LGNs, producing an on-centre and off-centre layer to replace the eye-specific layers (Morgan & Thompson, 1993). The on-layer is anterior and the off-layer is posterior, indicating that although the absolute positioning of cells is not genetically encoded, there is probably some bias (either through time of arrival or chemical gradients) to ensure that the on-leaflets are always anterior to the off-leaflets, in the same way that the contralateral eye always innervates layer A.

Similar enucleation experiments have been performed in the prenatal cat. After monocular enucleation at E44, both LGNs develop only two layers instead of the normal five. The dorsal layer is a so-called "magnocellular" layer, since it contains medium sized cells, and a ventral "parvocellular" layer with small sized cells. Also, the interlaminar gap between the two layers occurs in a novel position, rather than in the same position as one of the normal layers (Garraghty, Shatz, & Sur, 1988).

All of the previous experiments mentioned indicate that the retinogeniculate pathway is not simply defined by some genetic blueprint, but instead its development can be affected by various environmental factors. If the LGN can be affected by environmental factors, and if the retina is spontaneously active, can this activity also affect the development of the LGN?

2.8.3 Activity blockade experiments

The role of activity in the development of the retinogeniculate pathway has typically been investigated by blockade experiments, whereby the retinal activity is silenced in some way. The first set of experiments were performed in the neonatal kitten, blocking action potentials from one eye using intraocular injections of TTX (tetrodotoxin — a sodium-channel blocker) (Archer, Dubin, & Stark, 1982; Dubin, Stark, & Archer, 1986). Action potential blockade was maintained in one eye for the first twenty weeks of life whilst the other eye remained active. At the end of this period, individual relay cells from both LGN were examined. LGN cells in the deprived layer (layer A1 (or A) of the ipsilateral (or contralateral) LGN to the deprived eye) received mixed retinal inputs from both on- and off-centre retinal cells and both X and Y retinal cells. In comparison, cells in the non-deprived layer received inputs from only on- or off-centre cells and from only X or Y retinal cells. The blockade also caused the size of the geniculate layers to change: the non-deprived layer in each LGN increased in size (from 500 μm deep to around 800 μm deep) at the expense of the deprived layer (from 500 μm to 200 μm). The effect of action potential blockade was therefore to prevent the refinement of synaptic connectivity of the retinogeniculate pathway, causing geniculate cells to receive abnormal retinal input from mixed classes and for the non-deprived eye to innervate geniculate territory that should have been innervated by the deprived eye. Examination of retinogeniculate synapses showed that action potential blockade prevents their structural development, leaving them in an immature newborn state (Kalil, Dubin, Scott, & Stark, 1986).

The study by Dubin et al. (1986) only looked at early postnatal development, by which time eye-specific layers have already formed. More binocular cells were found in the experimental animals than the control animals, although they were mainly located at the border between layers A and A1 rather than throughout the whole lamina. A more appropriate experiment was performed by Shatz and Stryker (1988), blocking activity in both eyes by infusion of TTX above the optic chiasm during the period E42–58 when eye-specific layers form (Shatz, 1983). The effect of TTX on individual retinal axons was two-fold. First, axons from both eyes did not refine into their appropriate geniculate layer, but instead spread throughout much of the LGN preventing the development of eye-specific layers. Second, the terminal arbors of the axons were much wider than the normal thin column-like arbors. The existence of wide-branching arbors indicated that the retinotopic mapping was distorted (Sretavan, Shatz, & Stryker, 1988).

Similar blockade experiments have also been performed in the ferret to assess the role of activity in LGN development. The approach in these experiments was to block NMDA receptors in geniculate cells, since NMDA receptors have been hypothesised to play a role in detecting correlated retinal and geniculate activity (Constantine-Paton, Cline, & Debski, 1990). NMDA receptor blockade during the period P14–21 prevented the segregation of the geniculate into on- and off-leaflets (Hahm et al., 1991). Blockade of afferent activity with TTX application during postnatal weeks three to four also prevented the segregation into on- and off-leaflets (Cramer & Sur, 1997). The diffusible messenger nitric oxide is also required for segregation during this period (Cramer, Angelucci, Hahm, Bogdanov, & Sur, 1996). NMDA blockade was repeated in ferrets aged P1–7, the period when the LGN normally segregates into eye-specific layers (Linden et al., 1981). However, eye-specific layers still formed in the absence of NMDA receptor activation. Rather than ruling out the role of activity-dependent processes in eye-specific segregation, Smetters, Hahm, and Sur (1994) rightly concluded that there could be other activity-dependent mechanisms at work, or that the NMDA receptors are used to detect correlated activity for other purposes, such as topographic map refinement (Cline & Constantine-Paton, 1989).

2.8.4 Retinotopic map formation

The previous experiments have shown that many aspects of retinogeniculate development rely on neural activity. However, these experiments have only focused on the development of single cells within the pathway, without considering how the overall topography is affected. Unfortunately, experiments considering how the overall topography in mammalian visual system is affected by activity blockade are rare, looking instead at the development of single axon arbors (Sretavan et al., 1988; Simon, Prusky, O'Leary, & Constantine-Paton, 1992) and inferring from single axons how the overall topography might be affected.

Several experiments have been performed however in vertebrates to examine the role of activity-driven processes in retinotopic map formation. In developing frogs, NMDA receptor blockade prevents the refinement of the retinotectal map to such an extent that an area of tectum receives input from about four times the normal area of the retina (Cline & Constantine-Paton, 1989). This indicates that the role of activity may be to eliminate inappropriate synaptic connections, and that without the detection of correlated activity between retinal and tectal cells, mediated by NMDA receptors, the inappropriate retinotectal connections remain and the appropriate connections do not get strengthened.

Similar experiments have been performed in goldfish, following the regeneration of the retinotopic map after severing the optic nerve. After nerve crush, the optic nerve normally grows back into the tectum to reproduce a normal retinotopic map. TTX infusion during this regeneration period did not affect the overall retinotopic arrangement, but instead it dramatically increased the size of individual tectal receptive fields by around a factor of three. There was no difference in RGC receptive field size between the control and experimental animals, indicating that the larger tectal receptive field sizes are due to tectal cells receiving many more retinal inputs from a larger region of retina (Schmidt & Edwards, 1983). This again supports the notion that the inappropriate synaptic connections are not being eliminated by activity-driven processes.

If these principles can be applied to mammalian visual systems, it indicates that there are a combination of processes working together to form retinotopic maps. Since the overall topographic mapping in goldfish is not destroyed by activity blockade, some activity-independent process, such as chemical markers, must be guiding retinal axons to their targets. However, this can only produce a coarse-grained topographic mapping. The role of the activity-dependent processes is to refine this mapping by the selective reinforcement of synapses: inappropriate synapses are removed and appropriate synapses are strengthened (Goodman & Shatz, 1993).

Mechanisms of activity-driven processes

First of all, is the pattern of activity crucial for development, or is it just the presence (or level) of activity that initiates some other process, such as the release of nerve growth factors, that is responsible for development (Frank, 1987)? This hypothesis was tested by (Stryker & Harris, 1986) by replacing visually-induced activity with electrical stimulation of the optic nerves in kittens at a time when cortical ocular dominance is developing. When both nerves were stimulated simultaneously, ocular dominance columns in the cortex failed to develop. In comparison, asynchronous stimulation of the nerves induced the normal cortical ocular dominance patterns. The temporal pattern of activity, and not just its mere presence, is therefore important. The spatial pattern of activity is also important: exposure to stroboscopic illumination simultaneously activates most retinal cells and prevents the refinement of the topographic maps in goldfish, leaving tectal cells with abnormally large receptive fields (Schmidt & Buzzard, 1993).

Most ideas of activity-driven processes are centred around the principle that "cells which fire together should wire together". This is a common summary of the idea proposed by Hebb (1949) that if a presynaptic cell is connected to a postsynaptic cell and they tend to be active at the same time, the synaptic strength between them should be increased. Whether this principle is actually implemented in the nervous system is yet to be determined, although some evidence of this kind of plasticity (such as long-term potentiation and long-term depression) has been found in the hippocampus (Bliss & Lømo, 1973) and neocortex (Artola, Bröcher, & Singer, 1990; Friedlander, Frégnac, & Burke, 1993). Recent work in the developing retinogeniculate pathway has also shown that short bursts of stimulation can cause long lasting enhancement of synaptic transmission (Mooney, Madison, & Shatz, 1993; Mooney, Penn, & Shatz, 1995; Shatz, 1996). It is therefore likely that some form of Hebbian synaptic modification is taking place, although the fine details are yet to be worked out. In Chapter 3, the mathematical formulations of the Hebbian principle are discussed in more detail.

2.8.5 The need for activity-independent processes

Various experiments have just been described which summarise the evidence in favour of development being driven by activity-dependent processes. Are these processes alone sufficient to account for retinogeniculate development, and neural development in general? It is highly unlikely that everything is driven by activity-mediated processes for two reasons. First, activity blockade has been shown to have no effect on certain developmental processes. For example, TTX blockade in goldfish during the time when the optic nerve is finding its way to the optic tectum does not prevent the optic nerve reinnervating the tectum in the normal retinotopic manner (Schmidt & Edwards, 1983). Second, there are some forms of organisation which are unlikely to be solely formed by activity-driven processes. In the case of LGN development, the contralateral eye always innervates layer A and the ipsilateral eye always innervates layer A1. This is due to the relative advantage that the contralateral eye has, since it innervates the geniculate several days before the ipsilateral eye and can therefore innervate deeper into the geniculate. The difference in arrival times for axons from different eyes is an example of an activity-independent mechanism. At the sublaminar level, the on-leaflet is always anterior to the off-leaflet in the ferret. (In the case of segregation of on- and off-centre inputs, the mechanism responsible for the consistent ordering of the sublayers between animals is still unknown.)

It is therefore likely that a combination of activity-independent and activity-dependent processes are at work during different stages of development. The early development of the retinogeniculate pathway could be performed using activity-independent mechanisms, such as positional markers or chemical gradients (Yuasa, Hirano, Yamagata, & Noda, 1996; Rétaux & Harris, 1996), to create a coarse retinotopic mapping. This coarse mapping could then be refined or sharpened using activity-dependent processes which eliminate inappropriate synapses and strengthens topographically correct synapses. It is likely that this combination of early activity-independent processes followed by later activity-dependent processes apply to other pathways, both visual and non-visual (Goodman & Shatz, 1993).

2.9 Summary

This chapter has introduced the main elements of the early visual pathway in mammals from the retina to the geniculate, and from the visual cortex back down to the geniculate. The central hypothesis of this thesis has been introduced, stating that the LGN develops to a near-adult state using a combination of activity-independent and activity-dependent processes:

- Retinal axons from both eyes meet at the optic chiasm and project into the appropriate LGN using a combination of activity-independent markers (Hankin & Lund, 1991; Goodman & Shatz, 1993). The initial retinotopic map is quite coarse and most geniculate cells are binocularly driven.
- Spontaneous waves of retinal activity appear soon after the initial map is formed, and jointly refine the retinotopic map and cause geniculate cells to become monocular through Hebbian-like activity-dependent processes (Shatz & Stryker, 1988; Wong, Herrmann, & Shatz, 1991).

The main aims of the thesis are to investigate the form of these activity-independent and activity-dependent processes to see if they are sufficient to account for the refinement of ocular segregation and topography in the LGN. These processes are investigated using computer simulations of retinogeniculate development. In the next chapter, we review the main computer models of visual system development.