Casagrande, V.A. and **A.E.** Wiencken-Barger 2000 Developmental plasticity in the mammalian visual system. In ***The mutable Brain. Dynamic and Plastic Features of the Developing and Mature Brain.*** Ed. Jon H. Kaas, Harwood Academic Pubishers, The Netherlands, pp **1-48.**

1

Developmental plasticity in the .mammalianvisual system

V.A. Casagrande and **A.E.** Wiencken-Barger

1. INTRODUCTION

No one would argue with the statement that the nervous system of mammals is more plastic while it develops than when it matures. In fact, the term plasticity, defined as the "capacity for being molded or altered." (Page **648,** Merriam-Webster **1971)** takes its root from "plasia" meaning to form, develop or mold. This derivation also raises a question concerning the definition of ***developmental plasticity.*** Can one usefully distinguish between the two processes or are manipulations that reveal plasticity simply uncovering basic rules or mechanisms of normal development? In this chapter we will argue that it is useful to distinguish between these processes even though they may reflect common underlying mechanisms. We will define neural plasticity in development broadly as the potential for the maturing system to change its neural phenotype based upon altered patterns of connections or activity. We will focus on examples of plasticity in the development of the mammalian visual system, drawing upon studies of other systems where necessary to illuminate the mechanisms involved.

We will begin the chapter with a consideration of the technical limitations and assumptions that are necessary to interpret the reviewed results. Here we address the importance of species choice, including differences in maturation rate, maturity at birth, and potential for plasticity. In this section we **also** consider the relevance of understanding the sequence of maturation at different levels **of** the visual system at the time when any manipulation is made. Additionally, we address the limitations of the tools used **to** measure plasticity as well as the often unstated linking assumptions that are made between anatomy, physiology and behavioral manifestations of plasticity.

In the second section we review the normal development of the visual system. **Two** perspectives are emphasized in this section. First, we emphasize the conservation of

genetic programs and cell signaling pathways. Pathways that are critical for cell survival early in development are utilized at later stages to shape connections and respond to change. Second, development involves a series of steps in which cell fate becomes more restricted and the potential for plastic change more limited. Thus, a manipulation such as a lesion performed early in development (or at a stage when some component of the system is still very immature) has the potential to affect an entire cascade of developmental steps whereas the same lesion performed at a later stage will have more subtle effects.

In the third section we examine the plastic changes produced by different conditions of visual deprivation. Here we focus mainly upon the visual system changes produced by monocular or binocular deprivation, but also consider the effects of manipulating other aspects of the visual diet including stripe rearing and passive visual experience on the developing system. In this section, we also review studies showing the influence of lid suture or rearing with visual defocus on eye growth and the development of myopia, and address alternative mechanisms proposed to explain these peripheral visual system changes. At the end of this section we consider how mechanisms involved in early development discussed in the previous section can be invoked to explain the plastic changes seen following visual experience later in development.

In the fourth section we discuss studies of the effects of injury on the course of visual system development. We focus here on two types of injuries, namely, peripheral injury by loss of one or both eyes and central injuries where components of the visual pathway have been removed by lesions at various developmental stages. The studies of peripheral loss have noted many similarities to the effects of visual deprivation. However, eye loss often produces much more dramatic changes within the central targets of the retina than does visual deprivation. Central injuries can cause dramatic rewiring of the system especially if done at an early developmental stage. The most interesting cases involve situations where retinal axons are forced to grow into the somatosensory or auditory thalamus. These experiments raise interesting questions about the specification and plasticity of sensory cortex.

Finally, in the last section we attempt to map out the principal mechanisms that guide mammalian visual system development. We consider, in particular, the steps over time by which components of the system become committed to specific fates and connected to specific targets. The basic developmental mechanisms are highly conserved and are utilized early in development to establish the basic plan and later in development to allow for major or minor refinements of that plan based upon activity, normal or abnormal, or insult to the system.

2. ASSUMPTIONS AND TECHNICAL LIMITATIONS

How we define visual system plasticity will depend upon a variety of factors including: choice of species, stage of development, area of the nervous system examined, the tools we use to measure plasticity, and the assumed links made between levels of analysis including anatomy, physiology, and behavior. It is worth reviewing some of these factors and assumptions at the outset of our discussion.

2.1. Choice of Species

Although it is well recognized that vertebrates including mammals differ in sensory capacities, rates of development, and likely also the capacity for plastic modifications during development, it is often tacitly assumed that one can generalize results from one species to another. It is common to make the assumption that since the mammalian visual system arises from a common ancestor, the basic developmental programs and capacity for change are similar, differences reflecting only specializations needed for survival in particular environments. When simitar rules of development and capacities for plasticity are found in more than a single species, it increases the likelihood that common mechanisms apply. However, given that a very limited range of species is generally examined there is danger that inappropriate comparisons will be made. Cats, ferrets, rats and mice, and to some extent macaque monkeys most commonly have been used in studies of visual system development and plasticity. Moreover, results in these species often are compared to examples from the human clinical literature. This is despite the fact that all of these species are phylogenetically very distantly related, develop at different rates, and are specialized for very different visual niches. For example, it was assumed until very recently that the segregation of axons representing the two eyes into ocular dominance columns in primary visual cortex (V1) required appropriate visual experience in both cats and primates (see for review Hubel *et al.,* 1976, **1977,** LeVay *et al.,* **1978, 1980).** .This assumption was based primarily **on** work in **cats,** a species that is born before ocular dominance columns form and whose axons segregate into ocular dominance columns after lid opening. However, recent results in macaque monkeys in which the pathways from the two eyes were labeled prior to visual experience (via early Caesarian section) have shown that in this species segregation of axons into ocular dominance columns occurs ***before birth*** and does not necessitate visual experience (Horton and Hocking, **1996).** This finding also means that at least some of the plastic changes that are seen after early lid closure in' macaque monkeys represent sprouting of non-deprived eye axons and retraction of deprived eye axons that have already achieved segregation, not the maintenance of an early developmental exuberance. Since cats and ferrets are born before ocular dominance columns develop, their formation will always have the potential **to** be influenced by visual experience, unlike those in primates. In rats and mice **no** ocular dominance columns develop in visual cortex either normally or after any manipulation of the visual periphery at any age suggesting that this phenotype may be unique to certain species. Nevertheless, following early monocular lid suture rodents also exhibit electrophysiologically demonstrable shifts toward dominance of the open eye suggesting that they too show plastic changes with these developmental manipulations of visual experience (Gordon and Stryker, **1996).** At present the assumption is that all of these findings relate ultimately to common basic mechanisms that tie visual experience to axon growth or synaptic remodeling. However, these species differences raise a cautionary flag about the interpretation of specific phenotypes such as relative segregation of geniculate axons into ocular dominance domains in visual cortex.

2.2. Stages of Development and Critical Periods

Mammals are born at different stages of development and mature at different rates. These differences make cross-species comparisons difficult since there is no standard developmental yardstick. This issue was considered at length by Robinson and Dreher (1990), who suggested that if developmental events in the visual system are expressed as a proportion of the period between conception and eye opening, referred to as the "caecal period", a common timetable can be developed. The problem is that most investigators have not attempted to compare data according to this timetable. For example, it is quite common for investigators working with rodents to discuss manipulations relative to the day of birth such as the relative plastic changes seen after monocular eye removal at birth (Toldi *et al.*, 1996) without reference to the fact that results are comparable to enucleations that occur well before birth in primates and well after birth in any marsupial mammal. An additional issue concerns the relative rates of maturation. For instance, where the development of geniculocorticat axons in primates has been examined it has been shown that these axons still exhibit signs of normal growth (growth cones) three months after birth (Florence and Casagrande, 1990). This means that manipulations such as lid closure, which in primates are normally performed well before three months of age, are done during a time when geniculocortical axons are still in a normal growth mode even though bulk labeling studies (see above) suggest that they are well segregated into ocular domains at birth. In rats and cats manipulations of visual experience at three months would not be expected to influence growing axons which are relatively mature at this stage. In humans visual experience has been shown to influence visual system development for several years postnatal (Jacobson *et al.*, 1983). The issue is how comparable manipulations are in each of these species relative to the normal stages of maturation of the system. In order to adequately describe mechanisms of visual plasticity, it will eventually be necessary to understand and define normal stages of development in each model species.

2.3. Visual System Levels

Different levels and regions within levels of the visual system mature at different developmental stages and at different rates. For instance, in ferrets (a popular species used to examine visual system development and plasticity) neurogenesis within the ganglion cell layer of the retina, striate cortex, and lateral geniculate nucleus (LGN) all begin at approximately the same time, namely embryonic day 20 or 20 days post-conception (E20). However, neurogenesis ends at different times in each of these areas. Retinal ganglion cells are generated until postnatal day 2 (P2) (Greiner and Weidman, 1981), while LGN neurogenesis extends only until €30 (Peduzzi, t989) and visual cortex until 13 days after birth or postnatal day 13 (P13). Corticogeniculate cells are generated until E36, but the production of the layer IV cortical target cells of LGN axons peaks on this same day, and is not over until P1 (Jackson *et al.*, 1989). Within each of these regions there are also gradients of maturation such that areas representing central vision tend to mature ahead of those representing peripheral

vision (for review see Casagrande and Wiencken, 1996). Additionally, some functional classes of cells within each region are generated and begin to differentiate before others. Thus, in the ferret retina, medium ganglion cells (presumably X-cells or medium size W-cells) 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). This example is but one of many that could be cited (see also below) for the development of the visual system in different species. The point is that any manipulation within one part of the system during development (e.g., enucleation of one eye) will impact the remainder of the system in different ways depending upon the stage of differentiation of cells within that region. If manipulations of the periphery are done early enough, plastic changes seen centrally could reflect modifications in major developmental programs including, as we will describe below, cell birth, cell death and regional specification.

2.3.1. Technical Considerations

Clearly, descriptions and explanations of plastic changes within the developing visual system are limited by the devices used to measure such changes. Nevertheless, it is worth considering how some of these limitations may lead to incorrect interpretations. For instance, results of peripheral manipulations such as retinal lesions, lid suture deprivation, or induced strabismus are typically measured by recording extracellularly from visual cortical neurons in anesthetized paralyzed preparations. In these preparations anesthetics used vary but interact directly with either excitatory or inhibitory transmitters that are critical to the physiology of the cellular responses measured and also potentially to the induction of any short term plastic changes. Ketamine has been shown to inhibit glutamate receptors, neuroleptic drugs act as dopamine antagonists, barbiturates, propofol and a number of other popular anesthetics activate GABA receptors, and opioids act as agonists for presynaptic Ca^{2+} channels. In addition to the potential impact of the state of the animal on receptive field sizes, properties and responsiveness of cells, and potential for short term plasticity, extracellular recording does not allow for measures of synaptic inputs that do not result in measurable action potentials. Much has been made of "silent synapses" that become active following peripheral lesions resulting in enlargements or rearrangements of receptive fields (Rumpel *et al.*, 1998), yet these synapses may indeed be active but invisible to the typical extracellular electrode. Morphological measures of developmental plasticity have their own set of problems given that measures must be made in a very dynamic system where individual variations in growth patterns are extremely variable and statistically significant differences must be enormous. For example, Purves and Lamantia (1990) argued that during development of macaque monkey visual cortex, cytochrome oxidase (CO) blobs (the regular array of patches that mark functionally distinct cells in visual cortex of monkeys) increased in number postnatally. The original observations were based upon a small sample. Later these conclusions were retracted after larger samples showed unexpected variability in the normal sizes of visual cortex in developing and adult monkeys (Purves and Lamantia, 1993). Finally, large plastic changes attributed to changes at the cortical level may actually reflect smaller changes at earlier levels in the system where the relative sizes of structures are smaller as was shown in the somatosensory system by Florence *et al.*, (1998).

2.5. Linking Assumptions

Just as the techniques we use limit our views, our assumptions about the links between levels of analysis constrain our hypotheses about underlying mechanisms. In most instances we are faced with linking correlations between levels of analysis not proving causation. If an animal develops amblyopia following early monocular lid suture deprivation, LGN cells representing the deprived eye have small cell bodies and poorly developed axons in visual cortex, and cells in visual cortex respond poorly to the deprived eye, it is reasonable to assume a relationship. However there are many instances where correlations of this sort may lead to false conclusions. For instance, if a large unilateral lesion is made in the visual cortex (including areas 17, *18)* of an adult cat, that animal will appear blind within the opposite hemifield. Yet, as shown by Sprague decades ago (Sprague, 1966), vision can be restored by removing the opposite superior colliculus or by cutting the commisure between the colliculi. The interpretation of the latter result (now called the 'Sprague effect") was that the original homonymous hemianopsia was caused not by removal of visual cortex, per se, but by a subcortical imbalance in activity since bilateral cortical lesions produced only mild visual deficits in cats (Berkley and Sprague, 1979). Such issues of incorrect linking assumptions or correlations are even more of a problem following manipulations of the developing system where the manipulation itself may dramatically alter the maturation including the morphology and balance of activity of the entire system. Much of the literature on developmental plasticity is based upon correlations with many fewer studies employing rigorous tests of causation.

3. NORMAL DEVELOPMENT

In order to consider plastic changes within the developing visual system it is necessary first to outline the stages of normal development of the system. Construction of the nervous system occurs in a series of orderly steps in which cells become increasingly committed to specific fates with maturation. The very early phases of development of the visual system, during which broad regions of the nervous system are defined and the earliest connections established, do not require neural activity. The later phases in which axons, dendrites, and synapses are sculpted into the precise wiring seen in the adult require coordinated activity between cells although not necessarily visual experience. The visual system clearly is plastic during both phases of development but changes resulting from manipulations during each stage may involve different mechanisms depending upon the relative stage of commitment of the cells being manipulated.

3.1. Early Stages: Activity Independent Developmental Events

Regional specification of the nervous system including portions of the visual system begins very early before neural tube closure such that under the correct inductive signals specific zones of the anterior neural tube are specified to develop into the eye, lens placode, superior colliculus, etc. (see Rubenstein *et al.*, 1998). Currently an enormous array of transcription factors and extracellular signals have been identified that

are involved in these early stages of regional specification (Rubenstein and Shimamura, **1997).** Different neural components may be determined by distinct but interconnected genetic subprograms that are highly conserved across species suggesting some very powerful constraints on the regulatory relationships among genes that control early phenotypes. It has been hypothesized that regional specification *of* the forebrain, like the hindbrain, involves segmentation, in this case into a series of longitudinal and transverse segments defined by gradients in the expression of a number of genes (the prosomeric model) (Rubenstein and Shimamura, **1997).** Evidence for specification of some regions including the superior colliculus, pretectum, portions of the dorsal and ventral thalamus and hypothalamus appear to fit well with adult divisions; within the cortex these relationships are less clearly related to mature functional domains.

At these early stages of visual system development, alterations within the system can have dramatic affects on later growth. In that sense the system is much more plastic than at any later stage. Good examples of these relationships come from genetic studies of eye development in mouse, human, and fly (*Drosophila).* In mouse and human the paired box (*pax)-6/aniridia* gene and its homologue in flies, the ***eyeless*** gene, play major roles in eye and craniofacial development (Hanson and Van Heyningen, **1995;** Quiring ***et al.,*** **1994;** Ton ***et al.,*** **1991;** Hill ***et al.,*** **1991;** Halder ***et al.,*** **1995;** Xu ***et al.,*** **1999).** These genes control transcription factors that, in turn, regulate a cascade of other genes important for eye formation. Where loss-of-function mutations have been produced in .the ***eyeless*** gene, flies have either no eyes or very reduced or abnormal eyes. Similar phenotypes are seen with genetic knockouts or mutations in mice and humans, respectively. What is remarkable is that ectopic expression of either the fly ***eyeless*** gene or the mammalian homologue, ***pax 6,*** on imaginal discs of the fly leg or wing will result in fully formed eyes on these structures (Halder ***et al.,*** **1995).** These amazing results not only argue for a common evolutionary origin of eye development, but also reinforce the view that early developmental programs follow highly conserved rules of specification. These examples also underscore the dramatic effects that manipulations of any early developmental event can have on the organization of the rest of the system.

The next stage of visual system development in mammals is characterized by a series of steps whereby regions of the visual system (e.g., visual cortical areas 17 and 18) and cells within these regions become committed to their mature fates and positions. It is not the purpose of this chapter to review all of these steps in detail. However, several examples of the temporal sequence of events and potential mechanisms involved are relevant since any manipulations (e.g., enucleation) performed during this stage can potentially affect all subsequent stages in the development of the system. For examples of this intermediate stage of visual system maturation we turn to the development of the ferret (see Casagrande and Wiencken for review, **1996).** With the exceptions of birth date and rate of maturation the basic patterns of development are similar for other mammals. Ferrets are born 42 days post-conception (PO) and open their eyes 30 days postnatally (P30). As mentioned above, within the ferret visual system the first retinal ganglion cells, LGN cells, and area 17 cells are all "born" (i.e., have undergone their final cell division) at about the same time (E20-E22) (Jackson *et al.,* 1989; Peduzzi, 1989; Reese *et al.,* 1994). The

axons from these early-born cells immediately begin to extend towards their targets (Johnson and Casagrande, 1993; Taylor and Guillery, 1995).

. 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). Subsequent ganglion cells are generated in a rough central to peripheral gradient from E22-E32 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 the differences in the chronological development of different functional classes of ganglion cells that we described earlier (Reese et al., 1994). This ontogenetic sequence indicates that early in development some cells will have sent axons to their targets before others are even born. Furthermore, the leading wave of retinal axons at any moment in time will be made up of a restricted subset of the total from a roughly common retinal location and a common ganglion cell class.

In ferrets LGN cells are born between E20 and E30 (Peduzzi, 1989). However, more details of LGN generation are available in other species (Rakic, 1977, see for review Casagrande and Brunso-Bechtold, 1985). Functional retinal synapses in the LGN can be detected quite early in the cat, within a week after arrival of the first retinal axons (Shatz and Kirkwood, 1984). Therefore, since newborn LGN cells must first migrate from the ventricular zone to the lateral wall of the thalamus, it is likely that retinal axons make contact with the more mature LGN cells soon after they arrive at their appropriate location, without pausing for further development of the nucleus. As in the retina, LGN cells in ferrets extend axons soon after they are generated; these axons are evident in the internal capsule by E25 and below the cortical subplate (visual cortex anlage) by E27 (Johnson and Casagrande, 1993) see also Figure 1 (Figure 14 from Johnson and Casagrande, 1993).

In ferret visual cortex, the earliest born neurons (E20-E26) belong to a transient population of cells that reside within the developing marginal zone (MZ) and the subplate (SP) (Jackson et al., 1989). Neurons destined to form the other layers are born in an inside (layer 6) out (layer 2) pattern over a period extending from E22-P2. Transplantation experiments in ferrets indicate that early cortical neuronal progenitor cells are multipotent in early development and capable of producing neurons in different cortical layers depending on environmental cues; later dividing progenitors are less flexible (McConnell, 1988, 1992; Franz and McConnell, 1996). Commitment to a particular laminar fate occurs during the final cell division within the ventricular zone prior to migration; the local environmental cues that determine laminar fate remain to be identified (McConnell, 1988, 1992; Chenn et al. 1997; Bohner et al., 1997) (See Figure 2). Additionally, the earliest born cortical cells appear to play a special role in guidance of axons to and from the appropriate areas of cortex (for review see McConnell et al., 1994; Shatz, 1990; Casagrande and Wiencken, 1996). Deletion of subplate cells in ferret visual cortex has been shown to cause LGN axons to by-pass their target in cortex, although other cues must guide thalamic axons to the location of their targets initially (Ghosh et al., 1990).

Regional specification of cortex also occurs during this period (for overview see Chenn et al., 1997). Transplantation experiments in rats have shown that visual cortical neurons will take on characteristics of either motor or somatosensory cortical

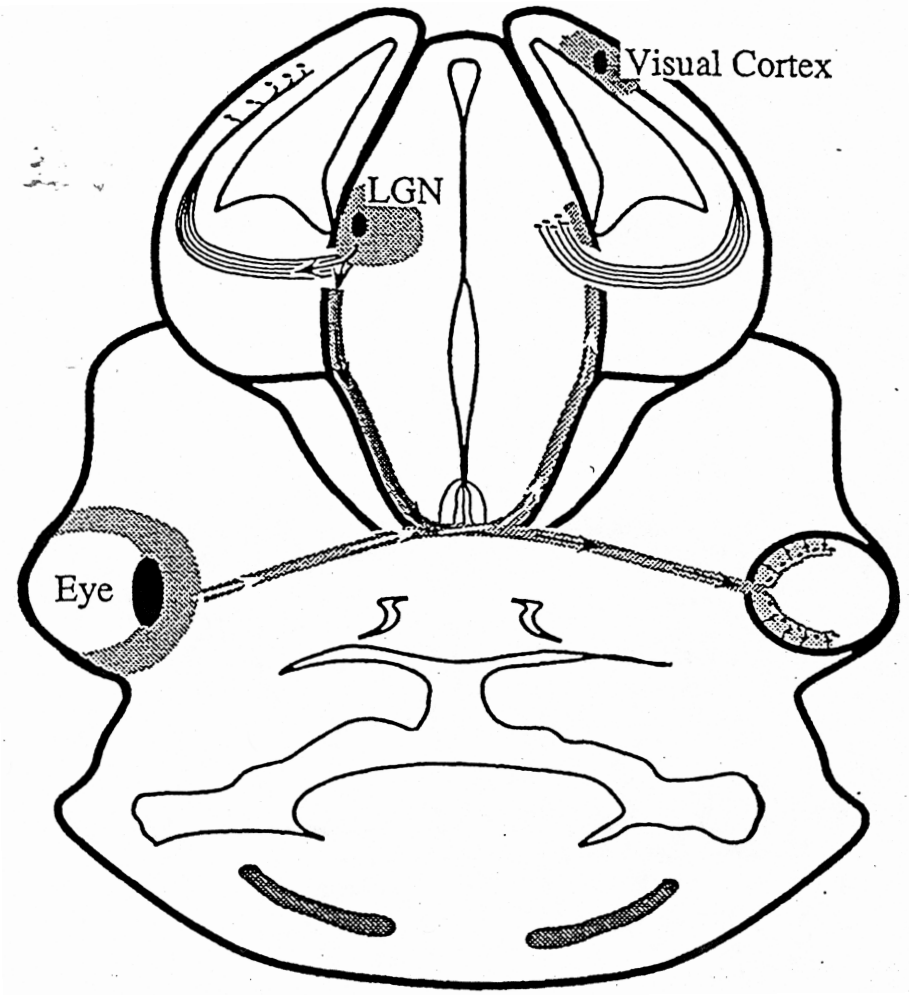

Figure 1 Schematic showing the pattern of connectivity between the retina and presumptive anlagen of the LGN and striate cortex in a ferret at embryonic day 27 (E27). Ferrets are born at **E42** and open their lids a month later. Retinogeniculate, geniculocortical, and corticogeniculate axons extend to their target structures by **E27.** White arrows show the path of DiA anterograde label along retinal axons from an eye inoculation of the dye. Black arrows show the path of retrograde label into the optic radiations and contralateral eye from an inoculation of DiI into the dorsal thalamus. Ipsilateral eye connections are not shown. Modified from Johnson and Casagrande (1993) with permission of the publisher.

neurons when transplanted to these regions in rats at the day of birth (PO) (Schlagger and O'Leary, 1993). Similar experiments performed with transplants of tissue between limbic and somatosensory cortex suggest that when regionally **specific** proteins (in this case ***Lamp)*** are expressed, cells are committed to exhibit basic characteristics of the region but are plastic before this point (Barbe and Levitt, 1992). At present, it appears that some aspects of regional specification in cortex depend both on intrinsic

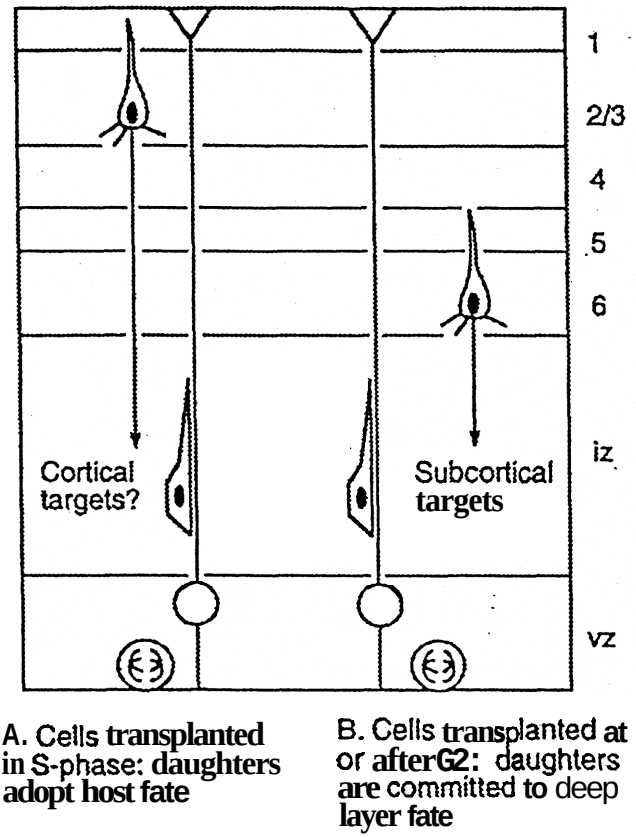

Figure 2 Cortical cell fate decisions. Layer 6 progenitor neurons adopt two different outcomes when transplanted into older host brains; in which upper layers neurons are being generated. **(A)** Cortical progenitors transplanted during **S** phase generate daughters that adopt the fate appropriate for neurons being generated **in** the **host** environment **while** those transplanted at or after G2(B) migrate to their normal deeper layers ***(5*** and 6) and form subcortical projections. These transplants suggest that there is a critical window of time early in the cell cycle during which progenitors receive environmental signals that determine their cortical laminar fate before they migrate. From McConnell (1992) with permission from the publisher.

programs and inputs from the thalamus (Chenn ***et al.*, 1997),** although many details **of** this specification process remain to be investigated. Moreover, recent studies examining cortical development in **Gbx-2** mutant mice that lack input from thalamus show that early neocortical regionalization can take place in the absence **of** thalamic innervation (Miyashita-Lin ***et al.*, 1999).**

During this early developmental stage and also later, vast numbers **of** cells die via programmed cell death **or** apoptosis. It is not within the purview **of** this chapter to cover the enormous literature on the topic of cell death ***(see*** Burek and Oppenheim, **1996;** Bergeron and Yuan, **1998 for** review). Suffice it to say that programmed cell death **or** apoptosis is thought to serve an important role in sculpting **the** developing nervous system

including the visual system of mammals. Manipulations performed during development can affect cell death programs by changing the proportion of cells that survive. These manipulations can affect one of three major cell death pathways. In neural development one of these pathways is activated specifically by the withdrawal of growth factors. Growth factor withdrawal leads to the release of cytochrome *C* from mitochondria which, in turn, results in activation of a cascade of cell death protreases known as caspases (Thornberry, 1998; Li *et al.,* 1998). A classic example comes from work in the peripheral nervous system in which it was shown that the normal excess of neurons produced during development competes for limited amounts of specific target derived survival factors, in this case nerve growth factor (NGF) (Barde, 1989, 1990; Oppenheim, 1991; Raff *et al.,* 1993). Within the visual system where 30–50% of cells are lost in the retina and central targets (Linden *et al.,* 1999) neurotrophins have also been implicated as survival factors (Frade *et al.,* 1999; Francis and Landis, 1999). Later in development and on into adulthood the same factors that played an early role in cell survival have been shown to subsequently play important roles in axonal refinement, synaptogenesis, plasticity,. and transmitter release in the maturing animal *(see* below).

3.2. Later Stages: Positional Cues and Activity Dependent Developmental Events

The next phase in visual system construction occurs in a series of steps that involve a variety of diffusable or membrane bound signals that help axons find their targets (Goodman and Tessier-Lavigne, 1997). Once axons arrive at their targets they seem to initially sort according to gradients of membrane bound molecules. These gradients help axons find their general addresses within the target. Axons respond differentially to cues at the target based upon their initial specification prior to axons outgrowth (e.g., nasal vs temporal retina); specification that can occur shortly after cell division (see above). Ganglion cell axons from different retinal locals therefore will respond differently to cues at the target based upon growth cone receptors. Good examples of this process have been described in monkeys where retinal axons that belong to different functional classes and developmental ages enervate appropriate LGN territories as soon as they arrive and, in the macaque monkey, before retinal ganglion cell death occurs (Snider *et al.,* 1999). The degree of early retinogeniculate axon targeting precision may vary between species since early retinal enervation of the ferret and cat LGN by retinal axons seems to be much less precise, although this difference may also reflect laminar mixing of functional classes in the adult LGN of these species (see Casagrande and Condo, 1988). Within the visual system the best studied example of axon sorting in relation to positional cues at the target is the retinotectal system. In both the retina and tectum several molecules have been identified that exhibit gradients (e.g. nasal/temporal or superior/inferior in the retina or within the corresponding map in the tectum). The most promising candidates for such positional cues are the Ephrin (Eph) family of receptor tyrosine kinases and their ligands (Cheng *et al.,* 1995; Drescher *et al.,* 1995; Tessier-Lavigne, 1995; Tessier-Lavigne and Goodman, 1996). Evidence indicates that ELF-1 protein (Ephrin-A2), a ligand for the Eph receptor tyrosine kinase, Mek4, that is expressed in a caudal-to-rostra1gradient, may guide retinal axons to their correct positions in the tectum *(See* Figure 3).

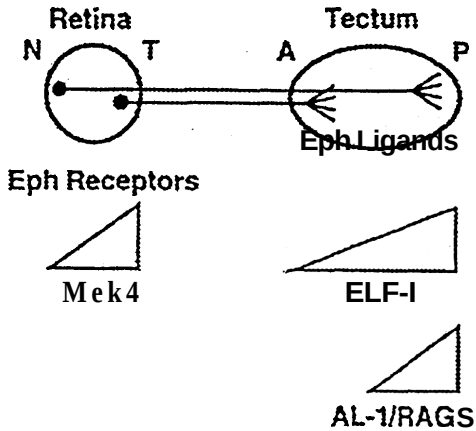

Figure 3 Eph ligands and receptors in the retinotectal system. Several Eph ligands are expressed in topographic gradients on the tectum, and appropriate Eph receptors are expressed in matching gradients on retinal neurons. ELF-1 is expressed in a gradient across the entire tectum, with highest expression in posterior (P) tectum. The ELF-1 receptor, Mek-4, is expressed in a gradient across the retina with highest expression in the temporal (T) retina, RAGS/AL-1 is expressed in a gradient across the posterior half of the tecum, with highest expression at the posterior end. N, nasal retina; A, anterior tecum. From Goodman and Tessier-Lavigne (1997) with permission of the publisher.

Once axons have sorted into their correct position, connections are refined based upon the coordinated neural activity of pre and postsynaptic cells (Katz and Shatz, **1996).** It is during this period that axon arbor remodeling and synaptic refinement occurs. It is also during this period (typically in the neonatal animal) that many experiments are done in an effort to define the potential of the system for plastic change (e.g., lid closure, enucleation, lesions). Examples of the role of neural activity during this phase of development come from numerous studies of retinogeniculate and geniculostriate systems in mice, ferrets, cats, tree shrews, and monkeys (e.g., mice: Antonini *et al.,* **1999;** cats and ferrets: Katz and Shatz, **1996;** tree shrews: Casagrande and Condo, **1988).** Retinogeniculate axons in which neural activity has been completely blocked do not sort into eye specific layers although the LGN cells themselves will eventually develop into layers from a uniform mass of cells; this event occurs only after a developmental delay once retinal axons are segregated (Casagrande and Condo, **1988).** Similarly in cortex, binocular blockade of activity prevents the normal segregation of geniculocortical axons in cats (Stryker and Harris, **1986).** It is likely that neither event requires visually driven activity since ocular segregation of axons in the LGN occurs before eyes open in all species studied, and in species such as macaque monkey ocular dominance columns in cortex form before birth (Casagrande and Brunso-Bechtold, **1985;** Horton and Hocking, **1996).** Experiments in cats and ferrets have demonstrated that prior to visually driven activity correlated waves of spontaneous activity already exist in the retina (Meister *et al.,* 1991; Wong *et al.,* **1993;** Weliky and Katz, **1999;** Cook et *al.,* **1999).** Neurons at this stage are coupled by developmentally transient gap junctions in both retina and visual cortex, and probably also other areas of the visual system (Kandler and Katz, **1995, 1998).** The waves of spontaneous

activity within the LGN, involving feedback from cortex or input from the eye, are important to competitive interactions that segregate the ocular inputs to the LGN into appropriate eye-specific layers since, as mentioned, blocking this activity in prenatal cats and postnatal ferrets disrupts the binocular segregation process (Shatz, 1990 for review). The role of spontaneous activity in the segregation of ocular inputs into ocular dominance columns in visual cortex remains to be tested but likely also will be found to involve correlated waves of spontaneous activity within the retinogeniculocortical circuit. In the examples cited above, activity likely affects the construction of new arbors and synapses more than the retraction of inappropriate connections, since the manipulations are initiated when retinal and geniculocortical axons still have a simple stick-like morphology (see Florence and Casagrande, 1990).

Specific pharmacological manipulations of activity performed while the visual system is developing have been shown to impact the maturation of the system selectively prior to the onset of visually driven activity. Treating the developing kitten retina with the glutamate analogue 2-amino-4-phosphonobutyrate (APB), which hyperpolarizes ON cone bipolar cells and rod bipolar cells, preventing their release of glutamate, arrests the dendritic stratification process; in the mature retina the dendrites of ON and OFF bipolar cells are segregated in the inner plexiform layer (Bisti *et al.*, 1998). Additionally, when kitten eyes are injected with TTX during the same period, the normal pattern of cell death that appears to produce a regular mosaic of ON and OFF ganglion cells is disrupted, suggesting that neural activity also plays a role in this process (Jeyarasasingam *et al.*, 1998). Early selective manipulations also have been shown to disrupt segregation of functionally distinct retinal axons in the LGN. In ferrets retinal axons in the LGN segregate into layers based both upon eye of origin and according to their response to the onset and offset of light. The segregation of retinal axons into ON and OFF sublaminae occurs after segregation of axons by eye. Both processes occur before eye opening but depend upon neural activity. Both forms of segregation appear to be blocked by intraocular injections of TTX. Although blockage of NMDA glutamate receptors in the LGN via infusion with MK-801 does not prevent the laminar segregation of retinal axons from each eye, it does prevent the segregation of ON and OFF axons into sublayers in the LGN (Smetters *et al.*, 1994; Cramer and Sur, 1997; Hahm *et al.*, 1991). These experiments illustrate the importance of activity, if not visually driven activity, during the establishment of the normal visual system.

3.3. Summary

Specification of visual system structures occurs very early before neural tube closure and involves highly conserved inductive signalling pathways that initially establish regional identity. Subsequently, the cells of the visual system become committed to specific fates at the time of final cell division. Molecular gradients, timing of axon arrival, and activity all help to shape early targeting decisions. Refinements of the system involve active growth and branching of axons and dendrites and formation of synapses as well as elimination of cells, axon collaterals, and some synapses. Refinements of visual system development depend upon activity but do not require

visual experience. However, visual experience can modify the final outcome as we will see in the next section.

4. DEVELOPMENT ALTERED BY SELECTIVE VISUAL DEPRIVATION

The potential for experience dependent plastic changes in the developing visual system has most often been measured by depriving animals of some aspect of their normal sensory environment at various postnatal ages. The most famous studies of this type were done by Wiesel and Hubel **(1963)** more than thirty years ago. They addressed the role of sensory experience on the development of visyal cortical neurons by either depriving kittens of patterned vision with monocular or binocular lid suture or normal binocular experience by cutting eye muscles to produce strabismus. These two forms of visual deprivation are now standard procedures used to examine the mechanisms of sensory plasticity. There have been a number of reviews that have covered different aspects of this vast topic (see LeVay *et* al., **1980;** Kiorpes and Movshon, **1996;** Fagiolini *et al.,* **1994;** Sherman and Spear, **1982;** Morrison *et al.,* **1998;** Tieman, **1991;** Crawford et *al.,* **1993;** Daw, **1998**). Therefore, in the section below we will consider selective examples of past and current findings on the plastic changes that occur following lid suture and other manipulations of early visual history. These examples will then to used to discuss alternative theories put forward to explain the outcomes.

4.1. Lid Closure: Central Changes

Visual deprivation produced by suturing the lid of one eye shut during early stages of visual experience can have profound effects on visual system development. Although some differences have been reported (see below), the basic changes within the visual system seen following lid closure early in life are similar across species. While some changes are evident at all levels of the visual system, the most profound effects on neuronal growth and activity have been described within visual cortex following monocular lid closure. These lid suture effects include domination of visual responses by the non-deprived eye, unequal growth of geniculocortical axons and geniculate cells driven by the deprived versus non-deprived eye, and changes (mainly although not exclusively down-regulation) of the expression of a variety of molecules including transmitters, peptides, and calcium binding proteins within cells driven directly or indirectly by the deprived eye and development of severe amblyopia in the deprived eye. These changes have been reported in a number of mammals, including: mice, rats, cats, ferrets, tree shrews, galagos, and monkeys (mice: Antonini *et al.,* **1999;** rats: Fagiolini *et al.,* **1994;** cats: Wiesel and Hubel, **1963,** Guillery and Stelzer, **1970,** Hubel *et al.,* **1977;** tree shrews: Casagrande *et al.,* **1978;** galagos: Casagrande and Joseph, 1980; monkeys: LeVay *et al.,* **1980).** In nonhuman primates, monocular eyelid closure has been used as a model to understand the mechanisms that produce certain forms of human amblyopia resulting from uncorrected infant cataracts, acute high myopia or ptosis (Von Noorden, **1978).** The much milder effects of rearing animals for short periods with both eyes sutured during early development have generally been

attributed to disuse (Wiesel and Hubel, **1963**; Hickey *et al.*, **1977**; Watkins *et al.*, **1978**; Antonini and Stryker, **1998**). The differences seen following monocular versus binocular lid closure led Hubel and Wiesel **(1965)** originally to propose that monocular suture results from the creation of a competitive imbalance between the geniculocortical axons from each eye; a point supported by their finding that geniculate cells innervated by the deprived eye are smaller than their non-deprived counterparts. The idea of binocular cumpetition was further supported by several additional studies showing that in either natural or artificially created monocular regions of the LGN, deprived LGN cells retain their normal size (Guillery and Stelzner, **1970**; Sherman *et al.*, **1974**). Since that time there have been literally hundreds of studies that have supported the idea that LGN axons from the two eyes compete for territory in visual cortex during normal development (see Antonini and Stryker, 1993). Early on it also was demonstrated that the important factor in monocular lid suture is not reduction in the amount of light reaching the retina or an imbalance in the number of photons reaching each retina but the elimination of patterned activity since the same effects can be produced with lenses that pass only diffuse light or blurred images (Wilson *et al.*, **1977**). Additionally, many studies have demonstrated that there is a critical period during development when lid suture effects can influence the development of the system; similar manipulations in adult mammals have only mild effects (Sherman and Spear, **1982** for review).

Efforts to understand the mechanisms underlying the plastic changes seen following monocular lid suture require an appreciation of what happens at each level of the visual system, the stage of development of cells at each level, and a detailed understanding of what changes and what does not change and whether effects generalize across species. Monocular deprivation has been shown to have effects at all levels of the visual system. Not surprisingly the effects are most dramatic in the portions of the system (e.g., visual cortex) that are least mature at the time of the manipulation, although relative developmental stage may not be the only reason for the differential effects seen. Also, the most profound effects are seen in binocularly enervated portions of the system where axons from the *two* eyes are in a position to interact or compete directly. At the level of the retina monocular deprivation has been shown to differentially influence the growth of different classes of retinal ganglion cells. For instance, in cats and tree shrews following early long term monocular deprivation, Y ganglion cells no longer are able to drive LGN cells (Sherman *et al.*, **1972**; Norton *et al.*, **1977**). In cats it has been shown that deprived Y ganglion cells lose collateral branches within the main LGN layers presumably because they compete within these layers with X cells for territory (Sur *et al.*, **1982**). The same argument has been made for the loss of Y cells in tree shrew LGN following monocular deprivation (Norton *et al.*, **1977**). In both species Y ganglion cells project to other central targets besides the LGN and so are not lost from the retina itself or optic nerve (Spear and Hou, **1990**). In primates where different classes of retinal ganglion cells project to separate layers of the LCN and are not in a position to compete directly there is no differential loss of ganglion cell projections to the LGN (Sesma *et al.*, **1984**). However, even in primate LGN (e.g., bush baby) M, P, and K ganglion cell axons are not morphologically normal following monocular deprivation and show changes in arbor shape, size, and bouton number (Lachica *et al.*, **1990**). These changes most likely reflect retrograde changes that

occur following cortical rearrangements since the physiological responses of deprived LGN M, P, and K cells and their inputs are normal in bush babies (Sesma *et al.* 1984) and show only mild changes in spatial and temporal thresholds in macaque monkeys. As mentioned above; monocular deprivation causes significant shrinkage of deprived LGN somata and changes in layer thickness in the deprived segment of LGN Layers. The morphological shape changes in ganglion axonal arbors within the LGN likely occur in response to the changes in the configuration of target dendrites in the LGN. (Lachica *er al.,* 1990).

The more dramatic changes that occur cortically as opposed to subcortically likely reflect the difference in maturity of retinal axons verses LGN axons; in all mammals studied, retinal ganglion cell axons are at a relatively mature stage of development by the time of normal lid opening (Lachica and Casagrande, 1988) and those from each eye are already segregated in the LCN (i.e., not in a position to compete) by the time of normal lid opening (Lachica *et al.,* 1990 for review). In contrast, even in primates geniculocortical axons are very immature at the time of normal lid opening and mature over an extended postnatal period (Florence and Casagrande, 1990). Changes in visual cortex can most readily be demonstrated at a time when geniculocortical axons are within a normal period of rapid growth and synaptic remodeling. In cats the most sensitive period (the critical period) for such effects is between 4 and 6 weeks, (the same period in rats extends between 20–35 days and in macaque monkeys from before birth to 8 weeks postnatal) (Daw *er al.,* 1992; Fagiolini *et al.,* 1994; Fox and Zahs, 1994; Hubel and Wiesel 1970; LeVay *et al.,* 1980; Littlejohn and Casagrande, 1994). During this peak period even short intervals of monocular deprivation have been shown to cause cortical cells to become unresponsive to the deprived eye and to change their morphology (Antonini and Stryker, 1993). Reverse suture during this period also appears to rapidly reverse these changes so that cortical cells now respond to the previously deprived eye (Sloper *et al.,* 1988; Smith *et al.,* 1982). Some of these changes can be accounted for by an active suppression of inputs from the deprived eye since in kittens the deprived eye can drive cells after either removal of the non-deprived eye or after blockade of GABAa receptors with bicuculline. (Kratz and Spear, 1976; Duffy *et al.,* 1976; Smith *et al.,* 1982; Mower *et al.,* 1984). These changes could also be accounted for if NMDA and AMPA receptors are regulated by activity in the manner described in cultured hippocampal neurons. Thus, as Liao *et al.* (1999) showed recently, immature hippocampal neurons mainly express NMOA receptors (synaptically silent) but progressively acquire AMPA receptors as the cultures mature. AMPA receptor blockade induced clusters of AMPA receptors whereas NMDA receptor bockade increased NMDA receptors. These changes suggest a means by which the number of silent synapses is regulated by changes in activity during development. Similar mechanisms could be invoked to explain rapid aspects of plastic changes in developing visual cortex.

Additionally, other details of cortical functional architecture can be modified by lid closure during the peak of the critical period. Monocular lid closure can degrade the orientation map driven by the deprived eye within the visual cortex of ferrets. Presumably the intrinsic wiring supporting orientation maps are not modified by this procedure since the orientation maps before deprivation and after recovery by reverse suture are identical (Kim and Bonhoeffer, 1994). Even after the critical period for anatomical modification of

geniculocortical architecture, late monocular lid closure can produce dramatic physiologically defined shifts in responsiveness of cells in the supragranular layers in cat cortex presumably because connections within these layers are still maturing (Mower and Christen, 1985). Moreover, even in the adult primate, plastic changes following brief periods of monocular deprivation can be demonstrated by rapid (within 5 hours) down regulation of the expression of the immediate early gene Zif268 within deprived eye columns extending through all the layers of primary visual cortex (Chaudhuri *et al.,* 1995), as well as, mainly down regulation of a variety of other molecules over longer periods (several days) including various transmitters (e.g., GABA, and glutamate), the synthesizing enzyme for nitric oxide (NOS), various neuropeptides and calcium binding proteins among others (see Morrison *et al.,* 1998 for review). However, in adults these changes are not translated into the growth related changes seen when the cortex is still maturing. Nevertheless, the latter results remind us that the visual system, like the rest of the nervous system, can be modified throughout life.

It has been argued from studies of cortical changes following monocular lid suture that the normal development of ocular dominance columns results from competitive interactions between the two eyes based upon an imbalance in visual experience (see above). However this scenario is unlikely, since ocular dominance columns form before birth in macaque monkeys (Horton and Mocking, 1996) and can form (although not completely) in cats that are dark reared or binocularly sutured from birth (see Mower *et al.,* 1985). It is also unlikely that other aspects of visual cortical architecture require visual experience to form since maps of orientation selectivity in visual cortex can be imaged optically in ferrets prior to visual experience (Chapman *et al.,* 1996). Thus, changes seen in these visual cortical properties following abnormal visual experience doubtless reflect modifications or refinements in a basic architecture that forms mainly without visual experience. Nevertheless, neural activity in form of waves of correlated spontaneous activity (Meister *et al.,* 1991; Weliky and Katz, 1999) may be important to the normal development of this architecture as discussed in the section above on normal development. The key to understanding the role of activity at each stage of development lies in the links between such activity and the final outcomes which range from alterations in synaptic strength to major modifications of cellular growth including all attendant cytoskelatal changes. Regardless, the fact that many mammals (e.g., ungulates) are born very precocial and capable of following their mothers and running with the herd within hours of birth reinforces the view the visual experience is unnecessary to the basic wiring of the normally developing mammalian visual system. Yet, it is equally clear that visual experience modifies and can fine tune this wiring. It follows that the developmental stage at which lid suture is performed is important to the outcome; one needs to remember that birth in different species occurs at different time points during development and proceeds at different rates (see above). This means that lid suture from birth in a primate occurs well *after* the eyelids have opened *in utero* and after the entire visual system is at a much more mature state than lid suture performed *before* the eyelids ever open in a cat, ferret, or rodent postnatally. This species difference also means that visual experience may normally have quite a different impact on the development of altricial mammals versus precocial mammals since the latter never "use" their systems until the system is relatively mature.

4.2. Binocular Suture and Dark Rearing

Deprivation by early binocular suture or dark rearing has both less severe (in the short term) and different consequences for the visual system as well as for the rest of the nervous system from monocular deprivation (Mower *et al.,* **1985).** Since useful vision is prevented equally in both eyes, activity dependent binocular interactions are balanced and no abnormal interactions occur comparable to those seen following monocular deprivation. However, prevention of useful vision during a critical growth phase when animals are able to interact with their environment can produce compensatory changes in other sensory systems which, in turn, may cause permanent rewiring within the visual system and subsequent behavioral blindness after long periods of deprivation (see Rauschecker **1997** for review). We will consider examples of some *of* these compensatory plastic changes in the sections below concerned with development altered by injury. Binocular suture is not the equivalent of dark rearing since the lids of the eye transmit diffuse light to the retina following binocular suture and thereby can activate cells in the retina including ganglion cells. In dark rearing the system develops without this form of stimulation and appears to remain more plastic (Mower *et al.,* 1985). Examples of key changes that occur following each of these forms of deprivation are compared below.

Both binocular suture and dark rearing for the first few weeks of a kitten's life significantly reduce the percentage of orientation and direction selective cells in visual cortex compared to normal controls but do not affect the initial development of ocular dominance columns (Frégnac, **1979;** Mower *et al.,* **1981;** Czepita *et al.,* **1994).** In both cases, however, ocular dominance columns are less well-developed than normal but clearly still present (Mower *et al.,* **1985).** After either binocular suture or dark rearing, animals appear blind but can demonstrate good visual recovery if the deprivation is short (Mower *et al.,* **1982).** Prolonged dark rearing in kittens (4–5 months or more) appears to degrade the ocular dominance columns that have already formed rather than allowing them to complete development as would be predicted if dark rearing simply slowed normal development (Cynader *et al.,* **1976;** Leventhal and Hirsch, **1980;** Swindale, **1981).** However, dark rearing does appear to prolong significantly the period *of* cortical plasticity for some manipulations. For example, monocular lid suture after 3 months of normal rearing does not cause a physiologically defined shift in ocular dominance toward the open eye, whereas a strong shift occurs if kittens are monocularly sutured after 4–5 months of dark rearing (Mower *et al.,* **1985;** Mower and Duffy, **1983).** However, interestingly, this shift is not accompanied by changes in the distribution of LGN afferents suggesting that the growth potential of these axons is limited to an early developmental period and that the physiologically defined shift in ocular dominance in cortical neurons can occur without light microscopically defined changes in the distribution *of* LGN afferents (Mower *et al.,* **1985). The** prolongation **of** the critical period by dark rearing has been used to try to tease apart factors that are critical for maintaining visual cortical plasticity. Exposure to light during dark rearing, even for just 6 hours (shorter intervals were not examined), was shown to be sufficient to eliminate plasticity in dark reared kittens (Mower *et al.,* **1983);** in these kittens monocular suture following dark rearing *is* no longer capable **of** shifting the distribution of cells that respond to the two eyes. Although the molecular switch that links

exposure to light to the termination of the critical period remains to be determined, it is known that several immediate early genes are upregulated in both adult and developing cats following dark rearing and light exposure. Behaviorally, long periods of binocular deprivation result in major visual deficits. Humans with removal of congenital cataracts as adults can demonstrate some visual recovery but must actively learn to make sense of their visual worlds (reported in Zeki, **1993).** Vision never becomes the dominant sense in these individuals suggesting that major rewiring has taken place (see also below).

4.3. Lid Closure: Eye Development and Myopia

Alterations in visual experience during development also can have profound effects on eye growth during development. More than 50 years ago studies of the distribution of refractive errors and myopia in human populations (Kempf *et al.,* **1928)** suggested that eye growth must depend to some extent upon visual experience. It was proposed that eye size is regulated by a feedback mechanism during development to ensure that images would remain in focus to achieve emmetropia in the adult (Tron, **1929;** Sorsby *et al.,* **1961;** O'Leary and Millodot, **1979;** McKanna and Casagrande, **1981;** for recent reviews see Norton **1999;** Raviola and Wiesel, **1990;** Wallman, **1990).** Subsequently, it was shown in tree shrews, monkeys, and chickens that deprivation of form vision through lid suture produced myopia and axial elongation in the deprived eye (Wallman er *al.,* **1978;** , Sherman *et al.,* **1977;** Wiesel and Raviola, **1977).** Because the experimentally produced myopia occurs only in the form deprived eye of animals and not in the non-deprived eye, genetic causes can be excluded. Potential artifacts associated with lid suture such as elevated temperature and potential changes in corneal shape produced by lid suture have also been ruled out (Norton, **1990).**

As with central plastic changes produced by manipulations of visual experience, there appears to be a critical developmental period during which eye growth can be affected by form deprivation. In tree shrews the susceptible period for deprivation peaks during the juvenile stage when the axial length of the eye is within about 7% of its adult value (Norton, **1990).** If normal vision is restored to the deprived eye during this critical period, axial elongation is slowed such that the retinal location now matches the shifted focal plane. The compensation in eye growth can be remarkably accurate and rapid (11 days in tree shrews) suggesting that there is an active and precise regulation of the axial length of the eye by visual experience (Siegwart and Norton **1998;** Hung *et al.,* **1995).** Additionally, the regulation of eye growth can occur independently within different portions of the eye. Depriving one half of the eye of either a chick or a tree shrew with a diffuse goggle can cause half of the eye to grow longer (Wallman *et al.,* **1987;** see for review Norton, **1999).**

What mechanisms are involved in these visually guided changes? The discovery of form-induced deprivation, recovery from induced myopia, and compensation for minus lenses placed in front of the eye has lent support to the hypothesis that an emmetropization mechanism exists. It was originally proposed that accommodation provided the driving force through a feedback loop in which defocus increased accommodation and produced increased pressure in the eye that resulted in axial elongation (McKanna and

Casagrande, 1981). Subsequently, however, it was demonstrated that cutting the optic nerve or blocking ganglion action potentials with TTX did not prevent the development of lid suture myopia in tree shrews and chickens (Norton et al 1994; Troilo *et al.*, 1987; McBrien et *al.*, 1995). From these data and other findings it has been argued that there must be a proximal mechanism by which retinal defocus results in the communication of signals from the retina directly to the sclera that produce changes in the scleral matrix (Norton and Rada, 1995; Gentle and McBrien, 1999). These signaling pathways could result in either increased elongation or slowing of eye growth depending upon the extensibility of the sclera (Siegwart and Norton, 1999; Wildsoet and Wallman, 1995). Since lathrytic drugs given systemically increase the severity of lid suture myopia, it is likely that the final common pathway involves some change in the collagen matrix which either allows for or prevents extensibility of the eye (McBrien and Norton, 1994). The intermediate signals between the retina and the collagen matrix are unknown. A number of signals have been proposed including several transmitters and growth factors. For example, retinal dopamine content has been found to be reduced 30% in myopic chickens (Stone *et al.*, 1990). Deprivation myopia is suppressed in both chickens and monkeys with the dopamine agonist, apomorphine. Curiously, however, deprivation myopia is also suppressed with administration of 6-hydroxy dopamine which kills dopaminergic cells (see Stone *et al.*, 1990). These conflicting data indicate that there must be other pathways involved. Some studies have suggested that cholinergic signals may be involved since atropine blocks deprivation myopia; however, recent data counters this argument (Fischer et *al.*, 1998). Moreover, these data are controversial since atropine could also act indirectly by blocking accommodation (McKanna and Casagrande, 1981). Rohrer and Stell (1994) suggest that basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGFβ) act as "stop" and "go" signals to modulate postnatal growth in the chick since the major biochemical change in chick associated with eye enlargement is an increase in scleral cartilage proteoglycan production (Marzani and Wallman, 1997). These ideas were tested with subconjunctival injections or intravitreal injections of bFGF, aFGF, and TGFβ. bFGF treatment at low doses slowed myopia development, aFGF was ineffective except at very high doses, TGF-beta had no effect except that it could inhibit the rescue effect of bFGF (see Rohrer *et al.*, 1997). One issue concerns the applicability of these data to mammals since, unlike chickens, mammals show the opposite effect, namely scleral thinning with deprivation myopia. Moreover, mammals have no scleral cartilage. At present, it is a matter of debate whether both a "stop" signal and a "go" signal is required for growth. In tree shrews the evidence suggests that there is only one signal required since developing eyes normally start *out* hyperopic (i.e., too short for the correct focus of the visual image) and move toward emmetropia and finally become myopic. Once they are myopic and the eye is beyond the emmetropic adult size, the myopia is not reversible (Norton, 1999). See Figure 4 for a proposed emmetropization model to account for normal and abnormal eye growth leading to myopia.

4.4. Other Manipulations of the Visual Diet

Although deprivation via lid suture or dark rearing are the most common experimental paradigms used to examine use dependent plastic changes, a variety of other conditions

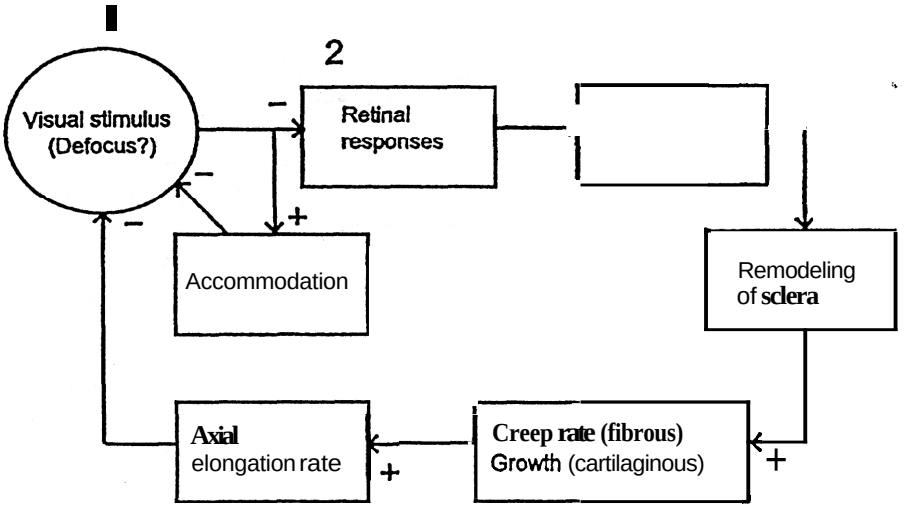

Figure 4 An emmetropization model: When axial length is shorter than the focal plane, defocus (1) occurs on the retina unless cleared by accommodation. Defocus reduces (–) the responsiveness of retinal neurons (2), altering the communication of signals (3) through the choroid to the sclera. When sufficient defocus is present, remodeling of sclera (4) increases, producing increased scleral creep rate (5) which increases the axial elongation rate (6) of the eye. Axial elongation moves the retina closer to the focal plane, reducing (–) the amount of defocus. As defocus is reduced on the retina, responses of retinal neurons increase, altering communication to the sclera. Scleral remodeling is reduced, creep rate is decreased and axial elongation slowed. This type of feedback model would produce the gradual axial lengthening and explain recovery from myopia if the defocus by the myopic eye was less than it would normally experience. See text for details. Figure from Norton (1999) with permission from the publishers, see also Siegwart and Norton (1999).

produce changes in visual system development. We briefly summarize the key effects of three such conditions here, namely strabismus, stripe rearing, and passive visual experience.

Strabismus: Uncorrected strabismus or deviation of the eye in children has long been known to lead to visual impairments which range from a mild deficit in stereoscopic vision to severe amblyopia in the deviating eye (Dobson and Sebris, **1989).** The differences in deficits seen appear to depend on the degree of useful vision provided by each eye. In cases where both eyes are used alternately, patients generally exhibit only a loss in stereopsis, whereas severe deviation of one eye, especially esotropia (eye deviates toward the nose), tends to result in amblyopia (Crawford et *al.,* **1993).** Cats and monkeys have both been used extensively as animal models of strabismus beginning with the early observations of Hubel and Wiesel **(1965)** that strabismic cats lacked binocular cells in visual cortex. The ocular dominance columns that form in cats with strabismus are more sharply defined than those seen in normal cats as would be predicted based upon models (e.g., Hebb, **1949;** see also below) that have proposed that separate synchronous barrages of activity within each eye result in postsynaptic activity in cortex that drives LGN afferents to segregate (Katz and Shatz, **1996).** Because binocular cells are normally located preferentially along the borders

between ocular dominance columns, it has been suggested that ocular dominance columns serve to organize the functional architecture underlying stereoscopic vision (Ferster, 1981; Le Vay and Voigt, 1988).

Experimentally produced strabismic amblyopia is normally created by cutting an extraocular muscle (Hubel and Wiesel, 1965; Von Noorden and Dowling, 1970; Harwerth and Levi, 1983), by injecting a muscle with botulinum toxin (Kiorpes and Movshon, 1989), or by use of prisms (Crawford and Von Noorden, 1979; Van Sluyters and Levitt, 1980; Mower *et al.*, 1982). As in humans strabismic monkeys and cats that develop a strong fixation preference become amblyopic in the deviated eye. Also as in humans, animals that alternate fixation develop normal resolution in each eye but binocularity is lost and lateral connections between adjacent ocular dominance columns in cortex is reduced presumably because the eyes are not used simultaneously (Löwel and Singer, 1992; Tychsen and Burkhalter, 1995). There is conflicting data in the literature over the physiological effects of artifically produced strabismus with some investigators demonstrating a strong shift in ocular dominance in animals that develop strabismic amblyopia and others reporting a normal binocular distribution of cells (Kalil *et al.*, 1984, Harrad *et al.*, 1996). Again species choice may make a difference in the results since the visual system of a cat at birth is comparable to a primate well before birth. It has been proposed that changes in interocular interactions that normally occur between binocular neurons involve intracortical inhibition which may than be strengthened as a result of rivalrous conditions between the *two* eyes (Sengpiel *et al.*, 1995; Sengpiel and Blakemore, 1996).

Stripe rearing: Two other manipulations of visual diet that result in plastic changes in the developing visual system are ***stripe rearing*** and rearing under conditions of ***passive stimulation.*** A number of attempts have been made to alter the proportion of visual cortical cells responding to different orientations by rearing cats either in striped environments or with goggles containing stripes of different orientations. Rearing with goggles can control for deviations of the head relative to the environment but are not equivalent to animals interacting with a striped environment as they move through that environment (Blakemore *et al.*, 1978; Stryker *et al.*, 1978; Gordon and Presson, 1982). Regardless, stripe rearing within the first few weeks'of a kitten's life has been reported to bias cortical cells toward the experienced orientation (Hirsch *et al.*, 1983). In addition, stripe rearing kittens with goggles modifies the dendritic morphology of cells in area 17 such that dendritic fields are asymmetric (Tieman and Hirsch, 1982). In the latter experiments kittens received 170 hours of exposure (an hour or more a day) beginning at 1 month of age; the kittens spent all non-exposure time in the dark. In kittens that viewed only vertical lines dendritic arbors were oriented perpendicular to the vertical meridian and in kittens reared with horizontal lines dendritic arbors were oriented parallel to the vertical meridian. Rearing cats in striped environments without goggles has also been shown to bias the orientation selectivity of the population of cortical cells but such studies have been heavily criticized based on the lack of control over the kittens' head movements and orientation (Stryker *et al.*, 1978).

Passive rearing: Passive visual stimulation in which'one developing kitten is carried in a sling on the end of a pole which is moved actively through the same environment by a sibling dramatically impairs the visual behavior of the passive kitten. As shown by Hein and colleagues (Hein and Diamond, 1972) kittens appear completely blind when

allowed to actively explore the same environment that they were moved through passively; these passively reared kittens consistently bump into objects and walls. The central changes that accompany such profound behavioral changes have never been fully explored but the results point to the importance of feedback to the normal development at least in species that are born at a very immature stage.

4.5. Proposed Mechanisms

How does the perturbation of visually driven neuronal activity influence neural development? A variety of pharmacological agents have been shown to influence the plastic changes in ocular dominance produced by lid suture. These include blockade of sodium channel activity with TTX, blockade of NMDA glutamate receptors, blockade of GABA, receptors, manipulation of levels of various neuromodulators and transmitters including serotonin, noradrenaline, acetylcholine, glutamate and cortisol, infusion of neurotrophins including BDNF, NGF, NT3 and NT4/5, lesions of intralaminar and medial dorsal nuclei of the thalamus, and anesthesia and paralysis (Stryker and Harris, **1986;** Kleinschmidt *et al.,* **1987;** Bear and Singer, **1986;** Daw *et al.,* **1991;** Carmignoto *et al.,* **1993;** Singer, **1982;** Shaw and Cynader, **1984;** Freeman and Bonds, **1979;** Maffei **et al., 1992;** Cabelli *et al.,* **1995;** for reviews see Daw *et al.,* **1995;** Cellerino and Maffei, **1996;** Hensch *et al.,* **1998).** The most popular explanation for how either spontaneous or evoked activity might modify cortical circuits is known as Hebb's **(1949)** postulate. Hebb proposed that the correlated activity of presynaptic and postsynaptic neurons would strengthen synaptic connections whereas uncorrelated activity would result in the weakening of connections. Hebb's hypothesis was originally formulated to explain learning and memory but has subsequently been applied to activity dependent synaptic development and plastic modification. If sets of correlated inputs tend to exclude uncorrelated inputs and are additionally constrained by molecular gradients related to retinotopy, then ocular dominance columns will form. This principle is best demonstrated in experiments where an extra eye was transplanted to the head of a developing frog (Constantine-Paton and Law, **1978).** In frogs each eye normally sends a crossed projection to each optic tectum. When a third eye is introduced, the two eyes are required to divide the tectal territory which they do by developing ocular dominance bands in the dually innervated tectum as would be predicted by the model.

The question then becomes what is the link between activity and neuronal growth or synaptic stabilization? Several molecular links have been proposed. We have already considered some of the mechanisms advanced to explain the link between retinal activity and eye growth. The most popular proposal to explain central effects of manipulations such as lid suture on the visual system is that molecules that are important for cell survival in early development (e.g., neurotrophins; see also above) and for learning and memory in the adult are also important in translating neural activity signals into process growth and synaptogenesis in late development (see Figure 5). The current model, again borrowed from models of learning and memory, is that activation of NMDA glutamate receptors during development is required for most synaptic stabilization. In this model during glutamate release the NMDA channel

opens only if the postsynaptic cell is sufficiently depolarized. Calcium ions that enter through the NMOA channel activate kinases in the postsynaptic cell. Through either kinase activation or some other calcium dependent mechanism, the postsynaptic cell becomes modified and more sensitive to transmitter release. A retrograde signal may be released that then influences the presynaptic cell possibly to release more transmitter. As discussed earlier a variety of neurotrophins have been implicated as important in visual system development, plasticity, and competitive interactions (Reichardt and Farinas, 1997). Any of these factors or a combination of factors could provide the necessary and appropriate signals. These signals could increase sensitivity to the transmitter in the postsynaptic cell as well as influence pathways involved in process growth and synaptic stabilization and release of transmitter in the presynaptic cell via a retrograde signal. Some data exist that support many aspects of such a model (see chapter in this volume by Bear). Early evidence in support of the NMDA hypothesis again came from work in the 3-eyed frog where infusion of the NMOA antagonist APV has been shown to block the segregation into ocular dominance bands (Cline *et al.*, 1987). Subsequently, a number of studies in mammals have supported aspects of the NMOA hypothesis or argued for NMDA-like mechanisms. For example, blockage of NMOA receptor activity prevents segregation of ON and OFF-center LGN axons in the ferret LGN (Hahm *et al.*, 1991) and also prevents the ocular dominance shift in visual cortex following lid suture in kittens (Bear *et al.*, 1990).

The link between NMDA and neurotrophins is less well established although it has been shown that BDNF and NGF can enhance the depolarization induced by the release of glutamate during the critical period for plasticity in rat visual cortex (Sala *et al.*, 1998). In visual cortex, infusion of the neurotophins BDNF and NT4/5, but not NGF and NT-3 has been shown to disrupt ocular dominance formation in ferrets (Cabelli *et al.*, 1995). The validity of this finding was strengthened by results showing that blockade of the trkB receptor for BDNF and NT4/5 via infusion of trkB-IgG also inhibits ocular dominance formation, whereas infusion of antibodies to neurotrophin receptors [i.e., trkA-IgG (NGF) and trkC-IgG (NT-3)] does not (Cabelli *et al.*, 1997). Although NGF infusion does not affect normal development of ocular dominance columns, its infusion does block the ocular dominance plasticity seen under a variety of abnormal conditions including lid suture, dark rearing, and strabismus (see Cellerino and Maffei, 1996 for review). How physiologically relevant these effects with NGF are remains controversial given that NGF and its trkA receptor, if present, are there at very low levels in the developing visual cortex, although their activation in rat visual cortex apparently prevents the effects of monocular deprivation (Pizzorusso *et al.*, 1999). Nevertheless, it is highly likely that neural development and plasticity within different regions of the visual system and at different time points are under the influence of several neurotophins. In visual cortex of neonatal ferrets studies by McAllister *et al.* (1995, 1999) have shown that BONF and NT-3 regulate dendritic development in different ways in different cortical layers. In layer 4 of visual cortex BDNF stimulated dendritic growth is inhibited by administration of NT-3. Within layer 6 these neurotophins demonstrated the opposite relationship to dendritic growth. There are various molecular pathways by which activation of trk receptors for neurotophins could selectively influence process growth generally via phosphorylation of specific tyrosine residues that create binding sites for the proteins Pi-3, PLC-γ, and

Shc, recruitment of which can result in neurite elongation, differentiation or further transcription via activation of MAP kinase pathways (Segal and Greenberg, 1996; see also Figure 6). The presence of high levels of neurotrophins and their receptors in many regions of neocortex and especially the hippocampus of adult brains suggests that these factors have important roles not only in development and plasticity in the

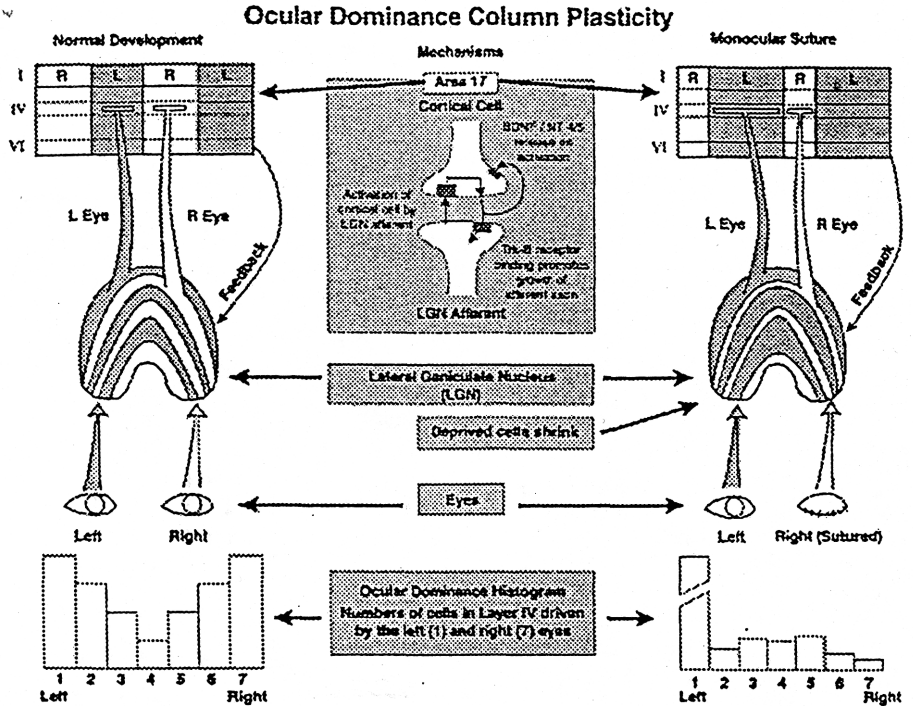

Figure 5 Changes within the LGN and visual cortex (area 17) seen following monocular lid suture in a macaque monkey. Axons from the left and right eyes segregate into 6 layers within the LGN early in development. LGN axons segregate into ocular dominance columns within layer IV of area 17. Axon segregation within the LGN and cortex take place before birth without visual experience. However, correlated spontaneous activity initially within each eye and subsequently via connections between segregated eye inputs in the LGN and cortex including corticogeniculate feedback (Weliky and Katz, 1999) may help axons segregate into ocular dominance territories. At birth LGN axons are very immature. Neonatal lid closure eliminates useful patterned activity within the sutured eye. As a result deprived LGN axons grow less and their LGN cell bodies shrink and non-deprived LGN axons expand more than normal. Since deprived LGN cell bodies within the monocular segments of the LGN do not show these changes it is likely that LGN axons innervated by the left (L) and right (R) eye compete within cortex for limited quantities of neurotrophic factors. Evidence (see text) suggests that the neurotrophins, brain derived neurotrophic factor (BDNF) or neurotrophin (NT) 4/5, are involved as shown in the center panel. These neurotrophins bind to tyrosine kinase receptor B (Trk-B) which can be located both pre- and postsynaptically. In this model activation of the cortical cell by axons would cause release of BDNF or NT4/5 which would act to promote growth and survival of the LGN axon. Neurotrophin release could also influence the dendritic growth of cells from which it was released via autocrine mechanisms. See also Figure 6 and text for details. Modifications of figure in Barker *et al.* 1999 with permission of the publisher.

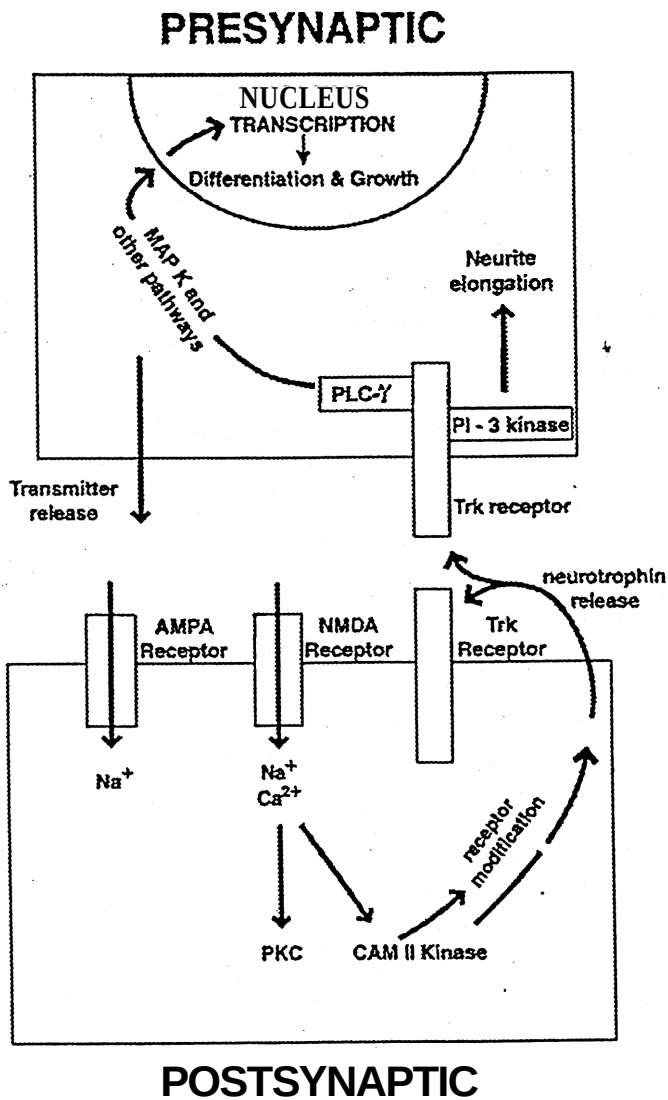

Figure 6 The **NMDA** receptor channel can open only during depolarization of the postsynaptic neuron from its normal resting level. Depolarization expels Mg^{2+} (not shown) from the **NMDA** channel allowing current to **flow** into the postsynaptic cell. Since the **NMDA** channel **is** permeable to Ca^{2+}, there is a significant Ca^{2+} entry into the cell which can trigger other events involving Ca^{2+}. Through either kinase activation (protein kinase C) or a separate Ca^{2+}-dependent mechanism (calmodulin kinase II) or other pathways, neurotrophins can be released from the postsynaptic cell that can act in **a** paracrine fashion to influence growth of the presynaptic cell/processes or **an** autocrine fashion to influence its own growth via pathways **shown** in the diagram for the presynaptic terminal/cell. Binding to neurotrophin Trk receptors causes them to phosphorylate tyrosine residues. Phosphorylation of specific tyrosine residues creates binding sites for PI-3 and Phospholipase C (Plc)-γ and recruitment of these proteins into a complex, thus initiating a signaling cascade that can lead to neurite elongation or via the MAP kinase pathway to transcription and ultimately differentiation and **growth.** See text for details.

maturing organism, by also in the adult, a perspective supported by studies showing that transgenic mice that lack BDNF show impaired LTP (Korte et *al.,* 1998).

5. DEVELOPMENT ALTERED BY INJURY

There are numerous studies that have demonstrated plastic changes in the visual system as a result of injury. It is not the purpose of this chapter to cover all of this vast literature in detail. Instead examples will be given of different classes of injuries and results that may shed light on mechanisms behind the plastic changes reported. in this section we focus first on results following monocular and binocular ennucleation. Plastic changes that result from eye loss share a number of features in common with examples given above on visual deprivation by lid suture. Second, we review findings on damage to central visual structures including lesions of the LGN, colliculus, and areas of visual cortex. As with the visual deprivation studies reviewed above, the relative state of maturity of the visual system and of other parts of the nervous system as well as species differences must be kept in mind in the interpretation of reported findings. Compensatory changes are generally assumed to be adaptive but are not in all cases. Additionally, it is clear that post injury experience plays a role in the degree of plastic change seen. This issue is also considered in the last section.

5.1. Ennucleation: Effects of Early Eye Loss

Monocular eye loss: If one eye is lost, removed, or fails to develop before major axonal pathways form in the visual system between the eye and its targets or between the LGN and visual cortex, major changes occur at all levels of the visual system. For example, monocular ennucleation prior to the time when retinal axons leave the eye blocks the ability of ipsilaterally projecting axons to reach the brain in mice and ferrets (Godement *et al.,* 1990; Guillery *et al.,* 1995). These temporal retinal axons apparently require the presence at the chiasm of crossing axons in order to advance past the chiasm to the brain since they stall at the chiasm and never enter the brain (Godement er *al.,* 1990). Monocular ennucleation done at a slightly later stage allows both t e m p ral and nasal axons from the remaining eye to reach their central targets. In the absence of axons from the other eye, brain targets receive input from only a subset of ganglion cells. In the case of species with a substantial uncrossed projection this means that some retinal targets (e.g., the LGN) receive input from only one half of each retina. Many of the changes seen following early monocular enucleation have been interpreted as demonstrating the importance of normally occurring competition between ganglion cells from the *two* eyes for a limited supply of trophic factors as described earlier for geniculocortical axons following monocular deprivation (Rakic, 1986). In keeping with this idea are findings that show that a percentage of ganglion cells that would normally be eliminated by cell death survive and the axons from the remaining eye cover territory that would normally be occupied by the ennucleated eye in both the LGN and superior colliculus (Garraghty *et al.,* 1986; Thompson *et al.,* 1993; Jeffery and Thompson, 1986; O'Leary et *al.,* 1986). However, closer inspection

of the changes that occur following early eye removal suggest that competitive interactions between axons from the two eyes may be limited by other factors (see Casagrande and Condo, 1988). For instance, in monocularly ennucleated tree shrews, ON-center and OFF-center uncrossed axons which normally innervate LGN layers 1 and 5, respectively, in this species appear to expand only into adjacent layers 2 and 4 and avoid terminating within zones occupied by layers 3 and 6 even though the latter territory is vacant (Casagrande and Condo, 1988). Layers 2 and 4 are normally innervated by crossed ON and OFF-center ganglion cells, while layers 3 and 6 are normally innervated by separate classes of crossed W-like cells. In tree shrews the crossed axons from the remaining eye form 4 layers, two wide layers that appear to be fusions of layers 1–2 and 4–5 and two relatively normal appearing layers, 3 and 6. The latter results as well as results from monocular enucleation studies in ferrets (Guillery *et al.*, 1985) suggest that under normal circumstances ganglion cell axons are restricted to terminating only within specific zones of the LGN and typically compete with ganglion cells of like type in the other eye or ganglion cells that normally occupy the same layer in the adult (see Figure 7 and Casagrande and Condo, 1988).

Monocular enucleation like monocular lid closure has dramatic morphological effects on the system only if performed during a critical period of development. If it is done during this window, whose limits have not been as clearly defined as for monocular deprivation but are likely to be similar, the entire visual system exhibits changes (Oppenheim, 1991; Chang et *al.*, 1995). If injury occurs early during this period increased cell death results within the LGN and superior colliculus. These changes have generally been documented by changes in tissue volume rather than cell counts due to difficulties in estimating cell death by such counts. In rats the colliculus and LGN contralateral to the enucleation shrink by 40 to 50% following early monocular enucleation (Lund et *al.*, 1973). In the cortex early monocular enucleation results in significant growth of arbors related to the remaining eye as well as expansion in callosal projections, and a lack of patchy tangential connections. (Ankaoua and Malach, 1993). In addition unique changes in retinotopy have been reported in some species following neonatal monocular enucleation. Trevelyan and Thompson (1992) report that ipsilateral to the remaining eye the visual cortex receives two convergent projections from the deafferented LGN, one mirroring the other in hamsters monocularly ennucleated on the day of birth (Krug *et al.*, 1998). In addition to the normal projection, a small population of cells within the ventral lateral portion of the nucleus send a second overlapping mirror image projection pattern to lateral cortex in this species. Map reversals have also been reported in the colliculus following prenatal enucleation but not postnatal enucleation in hamsters (Jeffery and Thompson, 1986). Since hamsters are born at a very immature stage of development when the first retinal axons have just entered the LGN and superior colliculus (Jhaveri *et al.*, 1991), it is possible that map rearrangements following enucleation result from interactions between growing temporal and nasal retinal axons prior to their innervation of their target. As mentioned above interactions with axons from the other eye are necessary for temporal axons to remain uncrossed at the chiasm in some species. If that is the case then the cortical changes seen may reflect abnormalities in the LGN map.

One of the more comprehensive efforts to understand the mechanisms driving change in cortex following early monocular enucleation has been done by Murphy

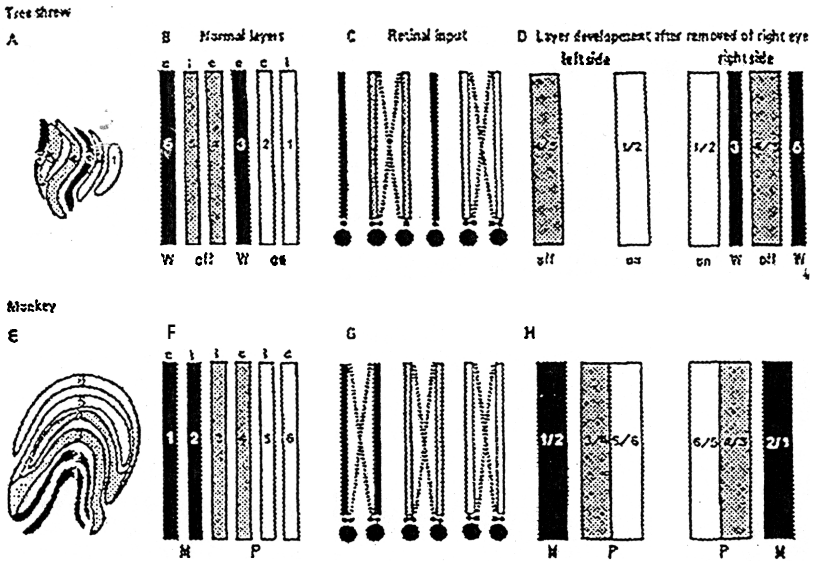

Figure 7 The normal pattern of LGN laminar organization in a tree shrew and a rhesus macaque monkey and the predicted changes in retinal afferent distribution following early unilateral eye ennucleation. **A** and **E** show semischematic drawings of a horizontal section through a normal tree shrew LGN **(A)** and a coronal section through a normal monkey LGN **(E).** Numerals represent individual cell layers and (with the exception of the W-like cell layers) shading patterns represent functionally matched sets of layers (i.e., tree shrew: ON center layers 1 and 2, **OFF** center layers **4** and **5,** and unique W-like layers **3** and 6; monkey: parvocellular **(P)** layers 3-6, and magnocellular **(M)** layers 1 and 2. **B** and **F** show the same arrangement in schematic form; I = ipsilateral retinal innervation; c = contralateral retinal innervation. **C** and G illustrate predicted interactions between separate functional classes of retinal **axons** following early unilateral eye removal for the tree shrew and monkey, respectively. **D** and **H** show the lamination pattern resulting from the predicted interactions indicated in panels C and G following enucleation of the right eye in the tree shrew and monkey, respectively. During development axons sort based upon individual identity (e.g., **P from M)** or location in the retina (e.g., nasal versus temporal) and presumed gradients of chemoattractive and chemorepulsive molecules within the LGN. Competitive interactions are not essential from initial segregation of these axons. Following early monocular ennucleation axons from the remaining eye show limited expansion into LGN territory normally occupied by **axons** of unlike functional class suggesting that under normal circumstances if binocular competitive interactions occur at all they are limited to **axons** of like type or axons that normally share territory within the same LGN layer. From Casagrande and Condo (1988) with permission from the publisher.

and colleagues (Clarke et ***al.,*** 1992; Murphy and Grigonis, 1988). In a series **of** papers they compared the callosal development of monocularly ennucleated rabbits with changes following monocular TTX eye injections, chronic cortical infusion of bicuculline to induce synchronized activity and systemic blockade of noradrenaline (NA) with injections of yohimbine (Clarke et ***al.,*** 1992; Murphy and Grigonis, 1988; Grigonis ***et al.,*** 1994). All treatments resulted in a more extensive callosal projection except following blockade **of NA** where the callosum **was** normal suggesting that **NA** plays a role **in** these plastic changes (see also above).

Binocular enucleation **like** dark rearing and binocular suture has effects that are distinct from those of monocular suture. And, although the possibility **of** binocular

competition is eliminated, that organism now must depend upon other senses which, in turn, results in compensatory changes in other systems and is followed by further changes within the visual system. If enucleation is performed very early prior to enervation of central structures the central effects can be profound. For example, Rakic and co-workers (1991) were able to demonstrate that the cortical respecification of parts of area V1 occurs following early prenatal enucleation in macaque monkeys such that a new histologically defined area (referred to as area X) developed with characteristics different from either V1 or V2. Following such early enucleations, as mentioned earlier, central retinal targets also are severely reduced in volume (Brunso-Bechtold and Casagrande, 1981; Brunso-Bechtold and Vinsant, 1984). Nevertheless, even if eye loss occurs before axons leave the retina, the remaining LGNs can still form topographic reciprocal connections with cortex, albeit less precise connections than normal (see Casagrande and Brunso-Bechtold, 1985; Guillery et al., 1985 for review)

A variety of biochemical and ultrastructual changes also occur after binocular enucleation. Changes include decreases in glucose utililization shown in rats both in visual cortex and in the LGN (Zilles et al., 1989), reduction in fatty acid incorporation suggesting reductions in phospholipases A2 and/or C (Wakabayashi et al., 1994), increases in serotonin, dopamine and norepinephrine in visual cortex (Lai et al., 1978), and higher turnover rates for dopamine, serotonin, and glutamate (Vizuete et al., 1993). In rats these changes are accompanied by a 20% loss of synapses and a comparable reduction in GABAergic terminals (Ribak and Robertson, 1986; Fifkova, 1970). No comprehensive picture of how these different changes relate to each other has been proposed.

The most interesting changes following early bilateral eye loss or binocular deprivation concern the induction of changes involving other sensory systems. Cases of congenitally blind humans that excel in tasks involving hearing and touch have been documented from the turn of the century (Diderot, 1916; Kellog, 1962; Niemeyer and Starlinger, 1981). Recently, using fMRI it has been shown that V1 and V2 become active in blind subjects while they read braille (Sadato et al., 1996). Additionally, in congenitally blind subjects interference with the function of the occipital cortex during braille reading using repetitive transcranial magnetic stimulation results in disruption of the braille reading skill (Cohen et al., 1997, 1999). Studies using other measures of blood flow and event related potentials in early blind humans also indicate that the visual cortex is activated by tactile information (Uhl et al., 1991, 1993). All of these studies suggest that the visual cortex may become rewired to respond to other modalities following early blindness.

Studies in animals also provide evidence for extensive rewiring of the visual and other sensory systems following early blindness caused by either congenital lack of eye development or eye removal. In cats early blindness results in auditory activation of the anterior ectosylvian visual area (normally a purely visual area) and sharpened tuning of auditory cells in auditory cortex (Rauschecker and Korte, 1993). Sound localization ability in early blind cats is also improved over normal (Rauschecker and Kniepert, 1994). In mice binocularly enucleated at birth the whisker representation in the somatosensory barrel field is enlarged (Rauschecker, 1997). Somatosensory evoked potentials have also been recorded in the visual cortex of enucleated rats (Toldi et al.,

1988). Toldi et *al.* (1994) also showed that maze performance of early ennucleated animals without vision was superior to that of controls. Early blindness not only affects central structures but has been shown to influence the growth of facial vibrissae which grow longer in cats deprived of vision from birth (Rauschecker et ***al.,*** 1992).

5.2. Cortical Lesions

As with early eye removal or visual deprivation the consequences of early damage to the central visual system of mammals can be dramatic system-wide changes that are not seen following similar damage in adult animals (for review see Payne and Cornwell, 1994; Spear, 1995; 1996). The reorganization of the system seen following early lesions often leads to reduced visual deficits when compared to deficits seen following comparable lesions in adult animals. The best studied examples of early central visual system lesions come from studies of damage to visual cortex including areas 17 and 18. Following neonatal damage to visual cortex changes have been reported in the retina, visual areas of the thalamus, midbrain, and within extrastriate cortex. Differences in rewiring and degree of functional recovery depend upon developmental age at the time of the lesion and species differences in maturation rate and in visual system organization and experience. Below we provide examples of major changes that occur following damage to area 17 in neonatal mammals.

In tree shrews, rodents, kittens, ferrets, and primates (e.g., galagos and humans) early postnatal damage or removal of area 17 (areas 17 and 18 in carnivores) has been shown to cause major cell loss within the retina and LGN, and in cats loss of cells in extrastriate areas that send axons back to area 17 (Dineen and Hendrickson, 1981; Weller *et al.,* 1981; Tong *et al.,* 1982; Calahan ***et al.,*** 1984). Within the LGN and retina cells that survive may be those that have collateral axonal branches terminating in other areas. In tree shrews removal of area 17 before the 3rd postnatal day results in almost the complete loss of LGN cells (Casagrande and Diamond, 1974). In cats removal of areas 17 and 18 and in macaque monkeys removal of area 17 also results in a massive class specific loss of LGN cells. Only LGN cells that send collaterals beyond the lesion site (Payne and Cornwell, 1994), some presumed koniocellular (K) cells in macaque monkeys (Hendrickson and Dineen, 1982), and some Y and W cells in cats survive. In the retina as in the LGN ganglion cells that send axons only to the LGN without collaterals to other locations are particularly vulnerable. In primates this means that all of the midget ganglion cells that project to the parvocellular layers of the LGN undergo cell death following early area 17 removal (Welter et *al.,* 1981). Similarly, removal of areas 17 and 18 at birth in kittens produces a 78% loss of X-cells the approximate percentage of X cells that project solely to the LGN (Callahan et ***al.,*** 1984); Y and W cells are preserved. In kittens older than 2 weeks or in adult cats similar lesions only produce a 22% loss of X cells (Callahan *et al.,* 1984). The greater vulnerability of developing ganglion cells to early cortical lesions could have several explanations. Since there have been reports of as much as an *80%* loss of ganglion cells in humans following long-standing damage to area 17 in adults, one possiblity is that degeneration of LGN target cells is simply more rapid following early lesions. Since degeneration in the LGN can be seen within days after an adult lesion in a cat or

primate this explanation seems unlikely. A more reasonable explanation is that rapidly growing axons such as the immature geniculocortical axons in cats and primates at birth are especially vulnerable to loss of neurotrophin support from their targets. Such an explanation is supported by experiments where neurotophins were infused following area 17/18 lesions in kittens resulting in a significant rescue of LGN cells (Cunningham *et al.*, 1987; Eagleson *et al.*, 1990; Agarwala and Kalil, 1998).

In addition to increased degeneration of LGN cells and ganglion cells, visual cortical lesions lead to rewiring of other pathways. As we describe below, if these lesions are combined with early midbrain lesions in ferrets and hamsters rewiring is very dramatic and includes other sensory systems. Following early ablation of visual cortex some "novel" pathways are established and other existing pathways expanded. In hamsters and tree shrews patches of retinal projections appear in the pulvinar following early cortical lesions; such projections are variably present normally (Schneider, 1973; Casagrande and Diamond, 1974). In cats where central rewiring following early lesions has been examined in detail by Payne and colleagues (Payne and Cornwell, 1994), several pathways show an increase in projection density (see also Kalil *et al.*, 1991; Tong *et al.*, 1991). These pathways include an enlarged projection to extrastriate areas via an expanded projection from the C laminae of the LGN to extrastriate areas (primarily W- cells) as well as expansion of the pathway from the superior colliculus to the lateral posterior nucleus to extrastriate cortex. In cats response properties of neurons in extrastriate areas (i.e., orientation selectivity) is similar to that of normal cats following infant lesions which is not the case following comparable lesions in adult animals (Guido *et al.*, 1990, 1992). Additionally, descending projections from extrastriate visual areas to the superior colliculus are expanded following early lesions of areas 17 and 18 in kittens (Kalil *et al.*, 1991). At present it is unclear how much rewiring of the central visual system takes place in other species. In primates only a few LGN cells send collaterals to extrastriate areas normally and these cells become much larger and may increase in number following early lesions yet other routes to extrastriate cortex via the superior colliculus could expand as reported in cats.

In terms of function, all species examined show more visual recovery from early restricted visual cortical lesions than from those inflicted later in life. However, if lesions are large and include extrastriate as well as striate visual areas then the prognosis for significant visual recovery is reported to be poor in all species even following infant lesions. Given the massive loss of ganglion cells reported following early lesions in primates and cats the degree of form and motion vision remaining in such animals is surprisingly substantial although visual resolution was not measured (see Payne and Cornwell, 1994). Even humans with early striate lesions demonstrate the capacity to follow moving objects, both achromatic and chromatic, and to judge direction and speed acurately (Cuo *et al.*, 1998). It seems likely that these additional visual capacities in humans also are the result of expanded pathways to extrastriate areas.

Why do immature brains respond differently to lesions than mature brains? In the case of the examples given above there may be a number of explanations. First, rewiring likely reflects the retention and expansion of existing collaterals that are present normally on immature axons but are pruned as the axon matures. For example, in hamsters it has been shown that developing retinotectal axons display

collateral side branches within several nuclei, collaterals that disappear as the axons mature (Jhaveri et *al.*, 1991). Similarly, in both developing cat and primate cortex maturing geniculocortical axons exhibit transient collaterals (Ghosh and Shatz, 1992; Littlejohn and Casagrande, 1994). Second, all demonstrated cases of rewiring involve neurons and their processes at a stage when they are in an active growth mode where major cytoskeletal remodeling is still taking place. Factors such as GAP43 that are found in actively growing processes within the immature system are not found within the adult visual system (Aarts et *al.*, 1998). Third, the potential for new growth is likely to be greater due to both the lack of growth inhibitory factors present in the mature system such as those present on mature astrocytes and oligodendrocytes (Schwab, 1996) and to the presence of higher levels of neurotophins or other factors not present in the mature case (see Bonhoeffer, 1996). Finally, neural activity likely plays a role in the recovery process since it has been demonstrated that mature animals with lesions of the visual system or other sensory systems compensate for damage only through practice (Will and Kelche, 1992; Rauschecker, 1997; Recanzone, et *al.*, 1992). Immature animals may be inclined to aid in their own the recovery due to other physiological factors that promote greater activity and exploration in the young.

5.3. Subcortical lesions

As with early visual cortical lesions, studies of subcortical damage show dramatic rewiring of the developing visual system. The most impressive examples of such rewiring come from studies in hamsters and ferrets by Angelucci et *al.* (1998) and Frost (1982, 1988, 1990), respectively following the lead of earlier studies by Schneidet (1979). In both hamsters and ferrets deafferentation of the medial geniculate nucleus (auditory relay) or ventral posterior nucleus (somatosensory relay) within a few days of birth can induce retinal axons to enervate these targets if the surgery is done early enough; both hamsters and ferrets are born when retinal axons are still very immature (Jhaveri *et al.*, 1991.; Johnson and Casagrande, 1993). The novel retinal projections produced by early deafferentation are likely to represent collaterals from a small subset of axons that also innervates a normal retinal target since no novel projections are produced without the presence of some normal retinal target tissue (Angelucci *et al.*, 1998), at least in the case of retinal projections to the medial geniculate nucleus of the ferret. In the ferret medial geniculate nucleus anaiysis of the patterns of these novel retinal projections suggest that they organize themselves into a retinotopic maps of eye specific patches. Only a very small subset of retinal W-cells appears to be capable to forming this anomolous projection in ferrets within a limited region of the deafferented medial geniculate nucleus. Angelucci *et al.* (1998) have provided evidence that the ectopic retinal collaterals compete with other brainstem axons for deafferented space within the medial geniculate nucleus, thus limiting the size of the projection. Similar limitations in extent of retinal axons to somatosensory and auditory thalamus in hamsters have been observed (Frost, 1982; 1986). The formation of these ectopic projections suggest that sensory axons are not rigid in their specification for targets within the thalamus. It seems likely that gradients of negative and positive guidance molecules that are relatively attractive/repulsive for specific

axons along with other factors such as timing and activity dependent competition (see above) ensure correct connectivity in the normal system. Given that ectopic retinal projections only form if deafferentation occurs very early in development it is also possible that such plastic changes reflect the maintenance of small exuberant collateral branches that occur only on immature axons (Jhaveri *et al.,* 1991; O'Leary and Terashima, 1988).

One of the most interesting issues that is raised by the production of novel retinal projections to the auditory and somatosensory thalamus is whether such plastic changes are functional. Studies examining the receptive field properties of auditory or somatosensory cortical target cells suggest that they may be, although unequivocal behavioral demonstrations that an animal can "see" with its rewired auditory or somatosensory cortex are not available. Studies of visual receptive fields in rewired ferret auditory cortex show that cells that would normally respond to auditory signals now exhibit many properties of visual cortical neurons including orientation, direction, and velocity sensitivity and simple and complex visual receptive field organization, properties not seen in the rewired medial geniculate nucleus (Roe *et al.,* 1993). These results could have several explanations. First, since cells that form ferret cortex are still being generated at birth, the ectopic retinal afferents could induce a local reorganization at the cortical level. Second, the visual properties that appear in auditory cortex may simply reflect the fact that intracortical circuitry or thalamocortical connections are very similar across areas. Finally, ectopic retinal axons may respecify their thalamic targets such that projections to cortex result in the visual properties seen. Transplantation studies where visual cortex of rats is transplanted to the location of ingrowing somatosensory afferents favors the idea that thalamic afferents can respecify pieces of cortex since under these conditions characteristics of somatosensory cortex (barrels) develop within visual cortex (Schlagger and O'Leary, 1993). However, the basic similarity in laminar architecture and cortical circuits across areas also argues that different tunes are played on the same piano depending upon input as does the finding that visual cortical like properties can be generated in both rewired somatosensory and auditory cortex (see Sur, 1993; Frost, 1990).

6. CONCLUSIONS AND SUMMARY

Major components of the visual system are regionally specified before neural tube closure. These regions express their specific fates under a cascade of inductive signals. Within these early stages the system has an enormous capacity for plasticity. Deletions of single genes (e.g., Pax 6) can cause major structural defects and rearrangements involving both neural and non-neural tissues (e.g., eye and craniofacial development). As development proceeds cells proliferate and influence each other's fates through an elaborate interplay of extrinsic and intrinsic signals. Cells then migrate forming the complex multilayered and nuclear structures that identify different portions of the adult visual system. Cells become committed to specific fates, such as laminar location in visual cortex, during their last cell division before they begin to migrate. Axon pathways are established through a variety of secreted factors and membrane bound molecules. Correct axon targeting involves gradients of chemoattractant and chemorepellent molecules as well as spontaneous activity. Major waves of cell death take place at this

stage which help to sculpt connections. Neural activity driven by visual experience is not required for basic aspects of axon targeting, map formation, segregation of axons into ocular territories within the LGN or area 17 at least in precocial mammals such as ungulates and primates. However, visual experience may normally impact early steps of visual system development in altricial mammals such as opossums, rats, mice, ferrets, and cats which are are all born at very early developmental stages. In all species abnormal visual experience through deprivation, peripheral or central damage, or rearing with restricted visual diets can profoundly alter the wiring of the system especially during the rapid axonal and dendritic growth phase. If damage occurs very early pathways can become respecified including rewiring across sensory modalities. Rapid changes in wiring only occur when processes are growing and likely involve the same cellular machinery that is used to establish and refine connections normally. The end of the critical period for major visual experience-related plastic changes in wiring of the visual system generally coincides with the point at which axons and dendrites within that part of the system (e.g., visual cortex) have reached maturity. Even the mature visual system can respond at all levels via expression of immediate early genes and regulation of a variety of transmitter and neuropeptide related molecules to conditions of visual deprivation and damage although the rapid growth related changes seen in developing animals are not seen.

Plastic changes within the visual system have been explained by Hebbian models in which correlated activity, either spontaneous or evoked, alters synaptogenesis and process growth though NMDA glutamate receptors, Ca^{2+} activated pathways and neurotrophins. These processes may be enhanced or inhibited by levels of a number of factors including levels of neuromodulators (e.g., acetylcholine, noradrenaline), cytokines, aspects of the extracellular matrix, and steroid hormone levels. Although similar mechanisms have been invoked to explain later occurring plastic changes in sensory systems, the plastic changes seen in response to damage or abnormal visual diets also clearly differ between the developing and adult mammals. Thus, abnormal visual diets such as monocular or binocular suture or strabismus can have a devastating effect if they occur before and during a critical window of development but not in the more mature animal. By the same token, mammals are better able to "compensate" for damage to parts of the visual system (e.g., visual cortex) if such damage occurs during specific windows of early life rather than at maturity. There are several factors that could explain these differences.

As discussed earlier levels of a variety of factors differ between mature and immature animals that could contribute to the degree of plasticity seen. it is clear that rapid changes in wiring only occur when the neuronal machinery for growth is switched on. Resistance to change may, in part, be explained by switching off mechanisms that control growth. For example, it is known that growth-associated protein (GAP)-43 levels drop and many receptors for neurotrophins switch to an inactive state with maturation (Katz and Shatz, *1996;* McIntosh *et al.,* 1990). in addition, numbers of NMDA receptors in visual cortex are lower in adults than in developing mammals. As axons mature and synapses stabilize changes in cell adhesion molecules (e.g., NCAM) and extracellular matrix also present barriers to major rewiring. Also, there are reported declines in acetylcholine and noradrenaline in cat visual cortex with age (Bear and Singer, 1986). As discussed above manipulating levels of either of these neuromodulators can influence ocular dominance

plasticity during development (Bear and Singer, 1986; Kasamatsu *et al.*, 1979; see also Daw, 1998).

Finally, plasticity differences between young and adult organisms may reflect the factors that drive a younger organism to seek a variety of forms of visual stimulation and to repeat visuomotor activities in ways more sedentary adult animals do not. Adult animals that are forced to use their visual systems via training show greater compensation for early damage. Understanding the neural mechanisms that drive early forms of visual self stimulation and how these factors interact with other mechanisms to allow for compensation from visual system damage will remain one of the challenges of the future.

ACKNOWLEDGMENTS

We are especially grateful to Vanessa Hill and Julia Mavity-Hudson for clerical and technical assistance and Michael Slowey for help with illustrations. This research was supported by NIH grants EY01778 (VAC) and core grants EY08126 and HD15052.

REFERENCES

Aarts, L.H., Schotman, P., Verhaagen, J. Schrama, L.H. and Gispen, W.H. (1998) The role of the neural growth associated protein B-50/GAP-43 in morphogenesis. *Advances in Experimental Medicine & Biology* 446, 85–106.

Agarwala, S. and Kalil, R.E. (1998) Axotomy-induced neuronal death and reactive astrogliosis in the lateral geniculate nucleus following a lesion of the visual cortex in the rat. *Journal of Comparative Neurology* 392, 252–263.

Agarwala, S. and Kalil, R.E. (1998) Long-term protection of axotomized neurons in the dorsal lateral geniculate nucleus in the rat following a single administration of basic fibroblast growth factor or ciliary neurotrophic factor. *Journal of Comparative Neurology* 392, 264–272.

Angelucci, A., Clasca, F. and Sur, M. (1998) Brainstem inputs to the ferret medial geniculate nucleus and the effect of early deafferentationon novel retinal projections to the auditory thalamus. *Journal of Comparative Neurology* 400,417439.

Ankaoua, D. and Malach, R. (1993) Evidence for plasticity of intrinsic horizontal connections in area 17 of the rat. *Israel journal of Medical Sciences* 29, 555–569.

Antonini, A. and Stryker, M.P. (1993) Rapid remodeling of axonal arbors in the visual cortex. *Science 260,* 1819–21.

Antonini, A. and Stryker, M.P. (1998) Effect of sensory disuse on geniculate afferents to cat visual cortex. *Visual Neuroscience* 15,401–409.

Antonini, A., Fagiolini, M. and Stryker, M.P. (1999) Anatomical correlates of functional plasticity in mouse visual cortex. *Journal of Neuroscience* 19, 4388–4406.

Barbe, M.F. and Levitt, P. (1992) Attraction of specific thalamic input by cerebral grafts depends on the molecular identity of the implant. *Proceedings of the National Academy of Sciences of the United Stares of America* 89,3706-3710.

Barde, Y.A. (1989) Trophic factors and neuronal survival. *Neuron* 2,1525–1534.

Barde, Y.A. (1990) The nerve growth factor family. *Progress in Growth Factor Research 2,* 237–248.

Barker, R.A., Barasi, S. and Neal, M.J. (1999) *Neuroscience at a glance.* Oxford, U.K.: Blackwell Science, Inc.

Bear, M.F. and Singer, W. (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* 320,172–6.

Bear, **M.F.,** Kleinschmidt, A. Gu, Q.A. and Singer, W. (1990) Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist. *Journal of Neuroscience* 10,909–925.

Bergeron, L. and Yuan, J. (1998) Sealing one's fate: control of cell death in neurons. *Current Opinion in Neurobiology* 8, 55–63.

Berkley, M.A. and Sprague, **J.M.**(1979) Striate cortex and visual acuity functions in the cat. *Journal of Comparative Neurology* 187,679–702.

Bisti, S. Gargini, C. and Chalupa, L.M. (1998) Blockade of glutamate-mediated activity in the developing retina perturbs the functional segregation of ON and OFF pathways. *journal of Neuroscience* 18,501 9–25.

Blakemore, C. Movshon, J.A. and Van Sluyters, R.C. (1978) Modification of the kitten's visual cortex by exposure to spatially periodic patterns. *Experimental Brain Research* 31,561 –572.

Bohner, A.P., Akers, R.M. and McConnell, S.K. (1997) Induction of deep layer cortical neurons in vitro. *Development* **124,** 915–923.

Bonhoeffer, T. (1996) Neurotrophins and activity-dependent development of the neocortex. *Current Opinion in Neurobiology* **6,** 119–126.

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. and Vinsant, S.L. (1990) An ultrastructural and morphometric study of the effect of removal of retinal input on the development of the dorsal lateral geniculate nucleus. *Journal of Comparative Neurology* 301,585–603.

Burek, **M.J.**and Oppenheim, R.W. (1996) Programmed cell death in the developing nervous system. *Brain Pathology* 6, 427–446.

Cabelli, R.J., Hohn, A. and Shatz, C.J. (1995) Inhibition of ocular dominance column formation by infusion of NT-4/5 or BDNF. *Science* **267,** 1662–6.

Cabelli, R.J., Shelton, D.L., Segal, R.A. and Shatz, C.J. (1997) Blockade of endogenous ligands of trkB inhibits formation of ocular dominance columns. *Neuron* 19, 63–76.

Callahan, E.C. Tong, L. and Spear, P.D. (1984) Critical period for the marked loss of retinal X-cells following visual cortex damage in cats. *Brain Research* **323,** 302–306.

Carmignoto, G., Canella, R. Candeo, P. Comelli, M.C. and Maffei, L. (1993) Effects of nerve growth factor on neuronal plasticity of the kitten visual cortex. *Journal of Physiology* **464,** 343–360.

Casagrande, V.A. and Diamond, I.T. (1974) Ablation study of the superior colliculus in the tree shrew *(Tupaia glis). Journal of Comparative Neurology* 156,207–237.

Casagrande, V.A., Guillery, R.W. and Harting, J.K. (1978) Differential effects of monocular deprivation seen in different layers of the lateral geniculate nucleus. *Journal* of *,Comparative Neurology* 179, 469–85.

Casagrande, V.A. and Joseph, R. (1980) Morphological effects of monocular deprivation and recovery on the dorsal lateral geniculate nucleus in galago. *Journal of Comparative Neurology* 194,413–26.

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,* 33–78. Ablox, Norwood.

Casagrande, V.A. and Condo, G.J. (1988) Is binocular competition essential for layer formation in the lateral geniculate nucleus? *Brain, Behavior & Evolution* 31, 198–208.

Casagrande, V.A. and Wiencken, A.E. (1996) Prenatal development of axon outgrowth and connectivity. *Progress in Brain Research* 108, 83–93.

Cellerino, A. and Maffei, L. (1996) The action of neurotrophins in the development and plasticity of the visual cortex. *Progress in Neurobiology* 50,333.

Chang, K., Van Sluyters, R.C. and Olavarria, J.F. (1995) Effect of monocular blockade of retinal activity on the development of visual callosal connections in the rat. *Biological Research* 28, 219–226.

Chapman, B. Stryker, M.P. and Bonhoeffer, T. (1996) Development of orientation preference maps in ferret primary visual cortex. *journal* of *Neuroscience* 16,6443–53.

Chaudhuri, A., Matsubara, J.A. and Cynader, M.S. (1995) Neuronal activity in primate visual cortex assessed by immunostaining for the transcription factor Zif268. *Visual Neuroscience* 12, 35–50.

Cheng, H.J., Nakamoto, M., Bergemann, A.D. and Flanagan, J.G. (1995) Complementary gradients in expression and binding of ELF-1 and Mek4 in development of the topographic retinotectal projection map. *Cell* 82,371–381.

Chenn, A., Braisted, J.E., McConnell, S.K. and O'Leary, D.D.M. (1997) Development of the cerebral cortex mechanisms controlling cell fate, laminar and areal patterning, and axonal connectivity. In: W.Maxwell Cowan, Thomas M. Jessell and S. Lawrence Zipursky, (Eds.) *Molecular and Cellular Approaches to Neural Development,* pp. 440-473. [New York, NY: Oxford University Press]

Clarke, R.J., Datskovsky, B.W., Grigonis, A.M. and Murphy, E.H. (1992) The effects of monocular enucleation on visual topography in area 17 in the rabbit. *Experimental Brain Research* 91, 303–310.

Cline, H.T., Debski, E.A. and Constantine-Paton, M. (1987) N-methyl-D-aspartate receptor antagonist desegregates eye-specific stripes. *Proceedings of the National Academy of Sciences of the United States of America* 84, 4342–4345.

Cohen, L.G., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., Dambrosia, J., Honda, M., Sadato, N., Gerloff, C., Catala, M.D. and Hallett, M. (1997) Functional relevance of cross-modal plasticity in blind humans. *Nature* 389, 180–183.

Cohen, L.G., Weeks, R.A., Sadato, N., Celnik, P., Ishii, K. and Hallett, M. (1999) Period of susceptibility for cross-modal plasticity in the blind. *Annals of Neurology* 45, 451–460.

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.

Constantine-Paton, M. and Law, M.I. (1978) Eye-specific termination bands in tecta of three-eyed frogs. *Science* 202, 639–641.

Cook, P.M., Prusky, G. and Ramoa, A.S. (1999) The role of spontaneous retinal activity before eye opening in the maturation of form and function in the retinogeniculate pathway of the ferret. *Visual Neuroscience* 16,491–501.

Cramer, K.S. and Sur, M. (1994) Blockade of afferent impulse activity disrupts on/off sublamination in the ferret lateral geniculate nucleus. *Brain Research,* 287–290.

Crawford, M.L. and Von Noorden, C.K. (1979) The effects of short-term experimental strabismus on the visual system in Macaca mulatta. *Investigative Ophthalmology.& Visual Science 18,* 496–505.

Crawford, M.L., Harwerth, R.S., Smith, E.L. and Von Noorden, G.K. (1993) Keeping an eye on the brain: the role of visual experience in monkeys and children. *journal of General Psychology* 120, 7–19.

Cunningham, T.J., Haun, F. and Chantler, P.D. (1987) Diffusible proteins prolong survival of dorsal lateral geniculate neurons following occipital cortex lesions in newborn rats. *Brain Research* 465,133–141.

Cynader, M., Berman, N. and Hein, A. (1976) Recovery of function in cat visual cortex following prolonged deprivation. *Experimental Brain Research* 25,139–156.

Czepita, D., Reid, S.N. and Daw, N.W. (1994) Effect of longer periods of dark rearing on NMDA receptors in cat visual cortex. *Journal of Neurophysiology* 72, 1220–1226.

Daw, N.W., Sato, H., Fox, K., Carmichael, T. and Cingerich, R. (1991) Cortisol reduces plasticity in the kitten visual cortex. *Journal of Neurobiology* 22, 158–168.

Daw, N.W., Fox, K., Sato, H. and Czepita, D. (1992) Critical period for monocular deprivation in the cat visual cortex. *journal of Neurophysiology* 67, 197–202.

Daw, N.W., Reid, S.N., Wang, X.F. and Flavin, H.J. (1995) Factors that are critical for plasticity in the visual cortex. [Review] [35 refs). *Ciba Foundation Symposium* 193,258–276.

Daw, N.W. (1998) Critical periods and amblyopia. *Archives of Ophthalmology* 116, 502–505.

Diderot, D. (1916) *Early Philosophical Works,* Chicago, IL: Open Court Publishing.

Dineen, J.T. and Hendrickson, A.E. **(1981)** Age correlated differences in the amount of retinal degeneration after striate cortex lesions in monkeys. ***Investigative Ophthalmology & Visual Science* 21, 749–752.**

Dobson, V. and Sebris, S.L. **(1989)** Longitudinal study of acuity and stereopsis in infants with or at-risk for esotropia. ***Investigative Ophthalmology & Visual Science* 30,1146–1158.**

Drescher, U., Kremoser, C., Handwerker, C., Loschinger, J., Noda, M. and Bonhoeffer, F. **(1995)** In vitro guidance of retinal ganglion cell axons by RAGS, a 25 kDa tectal protein related to ligands for Eph receptor tyrosine kinases. ***Cell* 82, 359–370.**

Duffy, F.H., Burchfiel, J.L. and Conway, J.L. **(1976)** Bicuculline reversal of deprivation amblyopia in the cat. ***Nature* 260, 256–257.**

Eagleson, K.L., Haun, F. and Cunningham, T.J. **(1990)** Different populations of dorsal lateral geniculate nucleus neurons have concentration-specific requirements for a cortically derived neuron survival factor. ***Experimental Neurology* 110, 284–290.**

Fagiolini, M., Pizzorusso, T., Berardi, N., Domenici, L. and Maffei, L. **(1994)** Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. ***Vision Research* 34, 709–720.**

Ferster, D. **(1981)** A comparison of binocular depth mechanisms in areas 17 and 18 of the cat visual cortex. ***Journal* of *Physiology* 311, 623–655.**

Fifkova, E. **(1970)** Changes of axosomatic synapses in the visual cortex of monocularly deprived rats. ***Journal* of *Neurobiology* 2, 61–71.**

Fischer, A.J., Miethke, P., Morgan, I.G. and Stell, W.K. **(1998)** Cholinergic amacrine cells are not required for the progression and atropine-mediated suppression of form-deprivation myopia. ***Brain Research* 794, 48–60.**

Florence, S.L. and Casagrande, V.A. **(1990)** Development of geniculocortical axon arbors in a primate. ***Visual Neuroscience* 5, 291–309.**

Florence, S.L., Taub, H.B. and Kaas, J.H. **(1998)** Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. ***Science* 282, 1117–1121.**

Fox, K. and Zahs, K. **(1994)** Critical period control in sensory cortex. ***Current Opinion in Neurobiology* 4,112–119.**

Frade, J.M., Bovolenta, P. and Rodriguez-Tebar, A. **(1999)** Neurotrophins and other growth factors in the generation of retinal neurons. ***Microscopy Research & Technique* 45, 243- 251.**

Francis, N.J. and Landis, S.C. **(1999)** Cellular and molecular determinants of sympathetic neuron development. ***Annual Review* of *Neuroscience* 22,541–566.**

Frantz, G.D. and McConnell, S.K. **(1996)** Restriction of late cerebral cortical progenitors to an upper-layer fate. ***Neuron* 17,** 55–61.

Freeman, R.D. and Bonds, A.B. **(1979)** Cortical plasticity in monocularly deprived immobilized kittens depends on eye movement. ***Science* 206,1093–1095.**

Fregnac, Y. **(1979)** Development of orientation selectivity in the primary visual cortex of normally and dark reared kittens. II. Models. ***Biological Cybernetics* 34, 195–203.**

Frost, O.O. **(1982)** Anomalous visual connections to somatosensory and auditory systems following brain lesions in early life. ***Brain Research* 255,627435.**

Frost, D.O. **(1986)** Development of anomalous retinal projections to nonvisual thalamic nuclei in Syrian hamsters: a quantitative study. ***Journal* of *Comparative Neurology* 252, 95–105.**

Frost, D.O. **(1990)** Sensory processing by novel, experimentally induced cross-modal circuits. ***Annals* of *the New York Academy of Sciences* 608, 92–109.**

Garraghty, P.E., Sur, M., Weller, R.E. and Sherman, S.M. **(1986)** Morphology of retinogeniculate X and Y axon arbors in monocularly enucleated cats. ***Journal* of *Comparative Neurology* 251, 198-215.**

Gentle, A. and McBrien, N.A. **(1999)** Modulation of scleral DNA synthesis in development of and recovery from induced axial myopia in the tree shrew. ***Experimental €ye Research* 68, 155–163.**

Ghosh, A., Antonini, A., McConnell, S.K. and Shatz, C.J. **(1990)** Requirement for subplate neurons in the formation of thalamocortical connections. ***Nature* 347,179–81.**

Ghosh, A. and Shatz, C.J. (1992) Pathfinding and target selection by developing geniculocortical axons. *Journal of Neuroscience* **12, 39–55.**

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.**

Godement, P., Salaun, J. and Mason, C.A. (1990) Retinal axon pathfinding in the optic chiasm: divergence of crossed and uncrossed fibers. *Neuron* **5,173–186.**

Goodman, C.S. and Tessier-Lavigne, M. (1997) Molecular mechanisms of axon guidance and target recognition. In: W.Maxwell Cowan, Thomas M.Jessell and S.Lawrence Zipursky, (Eds.) *Molecular and Cellular Approaches to Neural Development,* pp. **108–178.** New York, NY: Oxford University Press.

Gordon, B. and Presson, J. (1982) Orientation deprivation in cat: what produces the abnormal cells? *Experimental Brain Research* **46, 144–146.**

Gordon, J.A. and Stryker, M.P. (1996) Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *Journal of Neuroscience* **16, 3274–86.**

Greiner, J.V. and Weidman, T.A. (1981) Histogenesis of the 'ferret retina. *Experimental €ye Research* **33,315–332.**

Grigonis, A.M., Wang, Y. and Murphy, E.H. (1994) Systemic yohimbine prevents the exuberant callosal cell distribution in the striate cortex of the rabbit following monocular enucleation. *Soc for Neuroscience* **20,1109** (Abstract).

Guido, W., Spear, P.D. and Tong, L. (1990) Functional compensation in the lateral suprasylvian visual area following bilateral visual cortex damage in kittens. *Experimental Brain Research* **83, 219–224.**

Guido, W., Spear, P.D. and Tong, L. (1992) How complete is physiological compensation in extrastriate cortex after visual cortex damage in kittens? *Experimental Brain Research* **91, 455–466.**

Guillery, R.W. and Stelzner, D.J. (1970) The differential effects of unilateral lid closure upon the monocular and binocular segments of the dorsal lateral geniculate nucleus in the cat. *Journal of Comparative Neurology* **139, 413–421.**

Guillery, R.W., Ombrellaro, M. and LaMantia, A.L. (1985) The organization of the lateral geniculate nucleus and of the geniculocortical pathway that develops without retinal afferents. *Brain Research* **352, 221–233.**

Guillery, R.W., Mason, C.A. and Taylor, J.S. (1995) Developmental determinants at the mammalian optic chiasm. *Journal* of *Neuroscience* **15, t-37.**

Guo, K., Benson, P.J. and Blakemore, C. (1998) Residual motion dijcrimination using colour information without primary visual cortex. *Neuroreport* **9,2103–21**07.

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

Halder, G., Callaerts, P. and Cehring, W.J. (1995) Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila. *Science* **267, 1788–1792.**

Halder, G., Callaerts, P. and Cehring, W.J. (1995) New perspectives on eye evolution. *Current Opinion in Genetics & Development* **5, 602–9.**

Hanson, I. and Van Heyningen, V. (1995) Pax6: more than meets the eye. *Trends in Genetics* **11, 268-72.**

Harrad, R., Sengpiel, F. and Blakemore, C. (1996) Physiology of suppression in strabismic amblyopia. *British Journal of Ophthalmology* **80,373–377.**

Harwerth, R.S. and Levi, D.M. (1983) Psychophysical studies on the binocular processes of amblyopes. *American Journal of Optometry & Physiological Optics* **60, 454–463.**

Hebb, D.O. (1949) *The Organization of Behavior,* New York: Wiley.

Hein, A. and Diamond, R.M. (1972) Locomotory space as a prerequisite for acquiring visually guided reaching in kittens. *Journal of Comparative & Physiological Psychology* **81,394398.**

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

Hendrickson, A. and Dineen, J.T. (1982) Hypertrophy of neurons in dorsal lateral geniculate nucleus following striate cortex lesions in infant monkeys. *Neuroscience Letters 30,* **217–222.**

Hensch, T.K., Fagiolini, M., Mataga, N., Stryker, M.P., Baekkeskov, S. and Kash, S.F. **(1998)** Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science* **282, 1504–1508.**

Hickey, T.L., Spear, P.D. and Kratz, K.E. **(1977)** Quantitative studies of cell size in the cat's dorsal lateral geniculate nucleus following visual deprivation. *journal of Comparative Neurology* **172, 265–81.**

Hill, R.E., Favor, J., Hogan, B.L., Ton, C.C., Saunders, G.F., Hanson, I.M., Prosser, J., Jordan, T., Hastie, N.D. and Van Heyningen, V. **(1991)** Mouse small eye results from mutations in a paired-like homeobox-containing gene. *Nature* **355, 750.**

Hirsch, H.V., Leventhal, A.G., McCall, M.A. and Tieman, D.G. **(1983)** Effects of exposure to lines of one or two orientations on different cell types in striate cortex of cat. *Journal of Physiology* **337, 241–255.**

Horton, J.C. and Hocking, D.R. **(1996)** An adult-like pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience. *journal of Neuroscience* **16, 1791–807.**

Hubel, D.H. and Wiesel, T.N. **(1965)** Binocular interaction in striate cortex of kittens reared with artificial quint. *journal of Neurophysiology* **28, 1041–1059.**

Hubel, D.H. and Wiesel, T.N. **(1970)** The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *journal of Physiology* **206, 419–436.**

Hubel, D.H., Wiesel, T.N. and LeVay, S. **(1976)** Functional architecture of area **17** in normal and monocularly deprived macaque monkeys. *Cold Spring Harbor Symposia on Quantitative Biology* **40, 581–589.**

Hubel, D.H., Wiesel, T.N. and LeVay, S. **(1977)** Plasticity of ocular dominance columns in monkey striate cortex. *Philosophical Transactions of the Royal Society of London – Series 6: Biological Sciences* **278, 377–409.**

Hung, L.F., Crawford, M.L. and Smith, E.L. **(1995)** Spectacle lenses alter eye growth and the refractive status of young monkeys. *Nature Medicine* **1, 761–765.**

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. *journal of Neuroscience* **9, 1242–1253.**

Jacobson, S.G., Mohindra, I. and Held, R. **(1983)** Monocular visual form deprivation in human infants. *Documenta Ophthalmologica* **55, 199–211.**

Jeffery, C. and Thompson, I.D. **(1986)** The effects of prenatal and neonatal monocular enucleation on visual topography in the uncrossed retinal pathway to the rat superior colliculus. *Experimental Brain Research* **63, 351–363.**

Jeyarasasingam, G., Snider, C.J., Ratto, C.M. and Chalupa, L.M. **(1998)** Activity-regulated cell death contributes to the formation of ON and OFF alpha ganglion cell mosaics. *journal of Comparative Neurology* **394, 335–343.**

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. *Experimental Brain Research* **87, 371–382.**

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

Kalil, R.E., Spear, P.D. and Langsetmo, A. **(1984)** Response properties of striate cortex neurons in cats raised with divergent or convergent strabismus. *journal of Neurophysiology* **52, 514–537.**

Kalil, R.E., Tong, L.L. and Spear, P.D. **(1991)** Thalamic projections to the lateral suprasylvian visual area in cats with neonatal or adult visual cortex damage. *journal of Comparative Neurology* **314, 512–525.**

Kandler, K. and Katz, L.C. **(1995)** Neuronal coupling and uncoupling in the developing nervous system. *Current Opinion in Neurobiology* **5, 98–105.**

Kandler, K. and Katz, L.C. **(1998)** Coordination of neuronal activity in developing visual cortex by gap junction-mediated biochemical communication. *journal of Neuroscience* **18, 1419–1427.**

Kasamatsu, T., Pettigrew, J.D. and Ary, M. **(1979)** Restoration of visual cortical plasticity by local microperfusion of norepinephrine. *journal of Comparative Neurology* **185, 163–181.**

Katz, L.C. and Shatz, C.J. (1996) Synaptic activity and the construction of cortical circuits. *Science* **274, 1133-1138.**

Kellog, W.N. (1962) Sonor system of the blind. *Science* 399–404.

Kempf, G.A., Collins, S.D. and Jarman, B.L. (1928) Refractive errors in the eyes of children as determined by retinoscopic examination with a cycloplegic-Results of eye examination of 1860 white school children in Washington, DC. In: United States Public Health Service, (Ed.) *Treasury Department*, pp. 1-56. [Washington, D C United States Government Printing Office].

Kim, D.S. and Bonhoeffer, T. (1994) Reverse occlusion leads to a precise restoration of orientation preference maps in visual cortex *Nature* **372, 196.**

Kiorpes, L. and Movshon, J.A. (1989) Differential development of two visual functions in primates. *Proceedings* of *the National Academy of Sciences of the United States of America* **86, 8998-9001.**

Kiorpes, L. and Movshon, J.A. (1996) Amblyopia: a developmental disorder of the central visual pathways. *Cold Spring Harbor Symposia on Quantitative Biology* **61,** 39–48.

Kleinschmidt, A., Bear, M.F. and Singer, W. (1987) Blockade of "NMDA" receptors disrupts experience-dependentplasticity of kitten striate cortex. *Science* **238, 355-358.**

Korte, M., Kang, H, Bonhoeffer, T. and Schuman, E. (1998) A role for BDNF in the late-phase of hippocampal long-term potentiation. *Neuropharmacology* **37,** 553–559.

Kratz, K.E. and Spear, P.D. (1976) Postcritical-period reversal of effects of monocular deprivation on striate cortex cells in the cat. *Journal of Neurophysiology* **39, 501-511.**

Krug, K, Smith, A.L. and Thompson, I.D. (1998) The development of topography in the hamster geniculo-cortical projection. *Journal of Neuroscience* **18,** 5766–5776.

Lachica, E.A. and Casagrande, V.A. (1988) Development of primate retinogeniculate axon arbors. *Visual Neuroscience* **1, 103-123.**

Lachica, E.A., Crooks, M.W. and Casagrande, V.A. (1990) Effects of monocular deprivation on the morphology of retinogeniculate axon arbors in a primate. *Journal of Comparative Neurology* **296, 303-23.**

Lai, H., Makous, W.L., Quock, R.M. and Horita, A. (1978) Visual deprivation affects serotonin levels in the visual system. *Journal of Neurochemistry*. **30, 1187-1189.**

LeVay, S., Stryker, M.P. and Shatz, C.J. (1978) Ocular dominance columns and their development in layer IV of the cat's visual cortex: a quantitative study. *Journal of Comparative Neurology* **179,** 223–44.

LeVay, S, Wiesel, T.N. and Hubel, D.H. (1980) The development of ocular dominance columns in normal and visually deprived monkeys. *Journal* of *Comparative Neurology* **191, 1-51.**

LeVay, S. and Voigt, T. (1988) Ocular dominance and disparity coding in cat visual cortex. *Visual Neuroscience* **1,** 395–414.

Leventhal, A.G. and Hirsch, H.V. (1980) Receptive-field properties of different classes of neurons in visual cortex of normal and dark-reared cats. *Journal* of *Neurophysiology* **43,** 1111–1132.

Li, L., Prevette, D., Oppenheim, R.W. and Milligan, C.E. (1998) Involvement of specific caspases in motoneuron cell death *in vivo* and *in vitro* following trophic factor deprivation. *Molecular & Cellular Neurosciences* **12, 157-167.**

Liao, D., Zhang, X., O'Brien, R, Ehlers, M.D. and Huganir, R.L. (1999) Regulation of morphological postsynaptic silent synapses in developing hippocampal neurons. *Nature Neuroscience* **2,** 37–43.

Linden, R., Rehen, S.K. and Chiarini, L.B. (1999) Apoptosis in developing retinal tissue. *Progress in Retinal & Eye Research* **18, 133-165.**

Littlejohn, C.D. and Casagrande, V.A. (1994) Axon development in striate cortex (V1) of prenatal macaque monkeys. *Investigative Ophthalmology & Visual Science* **35, 1773** (Abstract).

Lowel, S. and Singer, W. (1992) Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science* **255, 209-212.**

Lund, R.D., Cunningham, T.J. and Lund, J.S. (1973) Modified optic projections after unilateral eye removal in young rats. *Brain, Behavior & Evolution* **8,** 51–72.

Maffei, L., Berardi, N., Domenici, L., Parisi, V. and Pizzorusso, T. (1992) Nerve growth factor (NGF) prevents the shift in ocular dominance distribution of visual cortical neurons in monocularly deprived rats. *Journal of Neuroscience* **12, 4651-62.**

Marzani, D. and Wallman, J. (1997) Growth of the two layers of the chick sclera ismodulated reciprocally by visual conditions. *Investigative Ophthalmology & Visual Science* **38, 1726–1739.**

McAllister, AK, Lo, D.C. and Katz, LC. **(1995)** Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron* **15, 791–803.**

McAllister, A.K., Katz, LC. and Lo, D.C. **(1999)** Neurotrophins and synaptic plasticity. *Annual Review* of *Neuroscience* **22, 295–318.**

McBrien, N.A. and Norton, T.T. **(1994)** Prevention of collagen crosslinking increases form-. deprivation myopia in tree shrew. *Experimental €ye Research* **59, 475–486.**

McBrien, NA., Moghaddam, H.O., Cottriall, CL, Leech, EM. and Cornell, LM. **(1995)** The effects of blockade of retinal cell action potentials on ocular growth, emrnetropization and form deprivation myopia in young chicks. *Vision Research.* **35, 1141–1152.**

McConnell, SK. **(1988)** Fates of visual cortical neurons in the ferret after isochronic and heterochronic transplantation. *journal of Neuroscience* **8,945–974.**

McConnell, S.K. **(1992)** The control of neuronal identity in the developing cerebral cortex. *Current Opinion in Neurobiology.* **2, 23–27.**

McConnell, SK, Ghosh, A. and Shatz, C.J. **(1994)** Subplate pioneers and the formation of descending connections from cerebral cortex. *journal* of *Neuroscience* **14, 1892–1907.**

McKanna, J.A. and Casagrande, V.A. **(1981)** Zonular dysplasia in myopia. In: Anonymous *Proceedings of the Second International Conference on Myopia,* pp. **21–32.**

McKanna, **J.A.** and Casagrande, V.A. **(1983)** Dark reared tree shrews do not develop lid-suture myopia. *Investigative Ophthalmology & Visual Science* **24, 226.**

McIntosh, H., Daw, N. and Parkinson, **D. (1990)** Gap-43 in the cat visual cortex during postnatal development. *Visual Neuroscience* **4, 585–93.**

Meister, M., Wong, R.O., Baylor, D.A. and Shatz, C.J. **(1991)** Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina. *Science* **252, 939–943.**

Merriam-Webster, A. **(1972)** *Webster's Seventh New Collegiate Dictionary,* Springfield, **MA:** *G.* & C. Merriam Company.

Miyashita, EM, Hevner, R, Wassarman, K.M., Martinez,. **S.** and Rubenstein, J.L.R. **(1999)** Early neocortical regionalization in the absence of thalamic innervation. *Science* **285, 906–9.**

Morrison, J., Hof, P.R. and Huntley, G.W. **(1998)** Neurochemical organization of the primate visual cortex. In: F.E. Bloom, A. Bjorklund and T. Hokfel, **(Eds.)** *The Primate Nervous System, Part II,* **299–430.** [Amsterdam The Netherlands: Elsevier Science B.V.]

Mower, G.D., Berry, D., Burchfiel, J.L. and Duffy, F.H. **(1981)** Comparison of the effects of dark rearing and binocular suture on development and plasticity of cat visual cortex. *Brain Research* **220, 255–267.**

Mower, G.D., Burchfiel, J.L. and Duffy, F.H. **(1982)** Animal models of strabismic amblyopia: physiological studies of visual cortex and the lateral geniculate nucleus. *Brain Research* **281, 311–327.**

Mower, G.D., Caplan, **C.J.** and Letsou, **G. (1982)** Behavioral recovery from binocular deprivation in the cat. *Behavioural Brain Research* **4, 209–215.**

Mower, G.D. and Duffy, F.H. **(1983)** Animal models of strabismic amblyopia: comparative behavioral studies. *Behavioural Brain Research* **7, 239–251.**

Mower, G.D., Christen, **W.G.** and Caplan, C.J. **(1983)** Very brief visual experience eliminates plasticity in the cat visual cortex. *Science* **221, 178-180.**

Mower, G.D., Christen, W.G., Burchfiel, **J.L.** and Duffy, F.H. **(1984)** Microiontophoretic bicuculline restores binocular responses to visual cortical neurons in strabismic cats. *Brain Research* **309,168–172.**

Mower, G.D. and Christen, W.G. **(1985)** Role of visual experience in activating critical period in cat visual cortex. *journal* of *Neurophysiology* **53,572–509.**

Mower, C.D., Caplan, **C.J.,** Christen, W.C. and Duffy, F.H. **(1985)** Dark rearing prolongs physiological but not anatomical plasticity of the cat visual cortex. *Journal of Comparative Neurology* **235, 448–66.**

Murphy, E.H. and Grigonis, A.M. (1988) Postnatal development of the visual corpus callosum: the influence of activity of the retinofugal projections. *Behavioural Brain Research* 30,151–163.

Niemeyer, W. and Starlinger, I. (1981) Do the blind hear better? Investigations on auditory processing in congenital or early acquired blindness. II. Central functions. *Audiology* 20, 510–515.

Norton, T.T., Casagrande, V.A. and Sherman, S.M. (1977) Loss of Y-cells in the lateral geniculate nucleus of monocularly deprived tree shrews. *Science* 197, 784–786.

Norton, T.T. (1990) Experimental myopia in tree shrews. *Ciba Foundation Symposium* 155, 178–194.

Norton, T.T., Essinger, J.A. and McBrien, N.A. (1994) Lid-suture myopia in tree shrews with retinal ganglion cell blockade. *Visual Neuroscience* 11, 143–153.

+Norton, T.T. and Rada, J.A. (1995) Reduced extracellular matrix in mammalian sclera with induced myopia. *Vision Research* 35,1271–1281.

Norton, T.T. (1999) Animal models of myopia: learning how vision controls the size of the eye. *ILAR Journal* 40, 59–77.

O'Leary, D.D., Fawcett, J.W. and Cowan, W.M. (1986) Topographic targeting errors in the retinocollicular projection and their elimination by selective ganglion cell death. *Journal of Neuroscience* 6, 3692–3705.

O'Leary, D.D. and Terashima, T. (1988) Cortical axons branch to multiple subcortical targets by interstitial axon budding: implications for target recognition and "waiting periods." *Neuron* 1, 901–910.

O'Leary, D.J. and Millodot, M. (1979) Eyelid closure causes myopia in humans. *Experientia 35*, 1478–1479.

Oppenheim, R.W. (1991) Cell death during development of the nervous system. *Annual Review of Neuroscience* 14, 453–501.

Payne, B.R. and Cornwell, P. (1994) System-wide repercussions of damage to the immature visual cortex. *Trends in Neurosciences* 17, 126–130.

Peduzzi, J.D. (1989) Neurogenesis of the geniculate nucleus in the ferret. *Soc for Neuroscience* 15, 1210 (Abstract).

Pizzorusso, T., Berardi, N., Rossi, F.M., Viegi, A., Venstrom, K., Reichardt, L.F. and Maffei, L. (1999) TrkA activation in the rat visual cortex by antirat trkA IgG prevents the effect of monocular deprivation. *European Journal of Neuroscience* 11, 204–212.

Purves, D. and LaMantia, A.S. (1990) Numbers of "blobs" in the primary visual cortex of neonatal and adult monkeys. *Proceedings of the National Academy of Sciences of the United States of America* 87,8185.

Purves, D. and LaMantia, A. (1993) Development of blobs in the visual cortex of macaques. *Journal of Comparative Neurology* 334,169–175.

Quiring, R., Walldorf, U., Kloter, U. and Gehring, W.J. (1994) Homology of the eyeless gene of drosophila to the small eye gene in mice and aniridia in humans. *Science* 265, 785–789.

Raff, M.C., Barres, B.A., Burne, J.F., Coles, H.S., Ishizaki, Y. and Jacobson, M.O. (1993) Programmed cell death and the control of cell survival: lessons from the nervous system. *Science* 262,695–700.

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. *Journal of Comparative Neurology* 176, 23–52.

Rakic, P. (1986) Mechanism of ocular dominance segregation in the lateral geniculate nucleus: competitive elimination hypothesis. *Trends in Neurosciences 9*, 9–11.

Rakic, P. (1991) Experimental manipulation of cerebral cortical areas in primates. *Philosophical Transactions of the Royal Society of London – Series B: Biological Sciences* 331, 291–294.

Rauschecker, J.P., Tian, B., Korte, M. and Egert, U. (1992) Crossmodal changes in the somatosensory vibrissa/barrel system of visually deprived animals. *Proceedings of the National Academy of Sciences of the United Stares of America* 89,5063–5067.

Rauschecker, J.P. and Korte, M. (1993) Auditory compensation for early blindness in cat cerebral cortex. *Journal of Neuroscience* 13, 4538–4548.

Rauschecker, J.P. and Kniepert, U. (1994) Auditory localization behaviour in visually deprived cats. *European journal of Neuroscience* 6,149–160.

Rauschecker, J.P. (1997) Mechanisms of compensatory plasticity in the cerebral cortex. *Advances in Neurology* **73,** 137–146.

Raviola, E. and Wiesel, T.N. (1990) Neural control of eye growth and experimental myopia in primates. *Ciba Foundation Symposium* **155,** 22–38.

Recanzone, G.H., Merzenich, M.M. and Jenkins, W.M. (1992) Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. *Journal of Neurophysiology* **67,** 1057–1070.

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

Reichardt, L.F. and Farinas, I. (1997) Neurotrophic factors and their receptors: roles in neuronal development and function. In: W. Maxwell Cowan, Thomas M. Jessell and S. Lawrence Zipursky, (Eds.) *Molecular and Cellular Approaches to Neural Development,* 220–263. New York, NY: Oxford University Press.

Ribak, C.E. and Robertson, R.T. (1986) Effects of neonatal monocular enucleation on the number of GAD-positive puncta in rat visual cortex. *Experimental Brain Research* **62,** 203–206.

Robinson, S.R. and Dreher, B. (1990) The visual pathways of eutherian mammals and marsupials develop according to a common timetable. *Brain, Behavior & Evolution* **36,** 177–195.

Roe, A.W., Garraghty, P.E., Esguerra, M. and Sur, M. (1993) Experimentally induced visual projections to the auditory thalamus in ferrets: evidence for a W cell pathway. *journal of Comparative Neurology* **334,** 263–280.

Rohrer, B. and Stell, W.K. (1994) Basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGF-beta) act as stop and go signals to modulate postnatal ocular growth in the chick. *Experimental Eye Research* **58,** 553–561.

Rohrer, B., Tao, J. and Stell, W.K. (1997) Basic fibroblast growth factor, its high- and low-affinity receptors, and their relationship to form-deprivation myopia in the chick. *Neuroscience* **79,** 775–787.

Rubenstein, J.L. and Shimamura, K. (1997) Regulation of patterning and differentiation in the embryonic vertebrate forebrain. In: W. Maxwell Cowan, Thomas M. Jessell and X. Lawrence Zipursk, (Eds.) *Molecular and Cellular Approaches to Neural Development,* 356–391. New York, NY: Oxford University Press.

Rubenstein, J.L., Shimamura, K., Martinez, S. and Puelles, L. (1998) Regionalization of the prosencephalic neural plate. *Annual Review of Neuroscience* **21,** 445–477.

Rumpel, S., Hatt, H. and Gottmann, K. (1998) Silent synapses in the developing rat visual cortex: evidence for postsynaptic expression of synaptic plasticity. *journal of Neuroscience* **18,** 8863–8874.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M.P., Dold, G. and Hallett, M. (1996) Activation of the primary visual cortex by Braille reading in blind subjects [see comments]. *Nature* **380,** 526–528.

Sala, R., Viegi, A., Rossi, F.M., Pizzorusso, T., Bonanno, G., Raiteri, M. and Maffei, L. (1998) Nerve growth factor and brain-derived neurotrophic factor increase neurotransmitter release in the rat visual cortex. *European journal of Neuroscience* **10,** 2185–2191.

Sato, T. (1957) *The Causes and Prevention of Acquired Myopia.* Tokyo Japan: Helarudo Printing.

Schlaggar, B.L., Fox, K. and O'Leary, D.D. (1993) Postsynaptic control of plasticity in developing somatosensory cortex. *Nature* **364,** 623–626.

Schlaggar, B.L. and O'Leary, D.D. (1993) Patterning of the barrel field in somatosensory cortex with implications for the specification of neocortical areas. *Perspectives on Developmental Neurobiology* **1,** 81–91.

Schneider, G.E. (1973) Early lesions of superior colliculus: factors affecting the formation of abnormal retinal projections. *Brain, Behavior & Evolution* **8,** 73–109.

Schneider, G.E. (1979) Is it really better to have your brain lesion early? A revision of the "Kennard Principle". *Neuropsychologia* **17,** 557–583.

Schwab, M.E. (1996) Structural plasticity of the adult CNS. Negative control by neurite growth inhibitory signals. *International journal of Developmental Neuroscience* **14,** 379–385.

Segal, R.A. and Greenberg, M.E. (1996) Intracellular signaling pathways activated by neurotrophic factors. *Annual Review of Neuroscience* **19,** 463–489.

Sengpiel, F, Blakemore, C. and Harrad, R. (1995) Interocular suppression in the primary visual cortex: a possible neural basis of binocular rivalry. *Vision Research* 35, 179-195.

Sengpiel, F. and Blakemore, C. (1996) The neural basis of suppression and amblyopia in strabismus. *€ye* 10, 250–8.

Sesma, M.A., Irvin, G.E., Kuyk, T.K., Norton, T.T. and Casagrande, V.A. (1984) Effects of monocular deprivation on the lateral geniculate nucleus in a primate. *Proceedings of the National Academy of Sciences of the United States of America* 81, 2255-9.

Shatz, C.J. and Kirkwood, P.A. (1984) Prenatal development of functional connections in the cat's retinogeniculate pathway. *journal of Neuroscience* 4, 1378-1397.

Shatz, C.J. (1990) Impulse activity and the patterning of connections during CNS development. *Neuron* 5, 745-756.

Shaw, C. and Cynader, M. (1984) Disruption of cortical activity prevents ocular dominance changes in monocularly deprived kittens. *Nature* 308, 731-734.

Sherman, S.M., Hoffmann, K.P. and Stone, J. (1972) Loss of a specific cell type from dorsal lateral geniculate nucleus in visually deprived cats. *journal of Neurophysiology* 35, 532-541.

Sherman, S.M., Guillery, R.W., Kaas, J.H. and Sanderson, K.J. (1974) Behavioral, electrophysiological and morphological studies of binocular competition in the development of the geniculo-cortical pathways of cats. *journal of Comparative Neurology* 158, 1–18.

Sherman, S.M., Norton, T.T. and Casagrande, V.A. (1977) Myopia in the lid-sutured tree shrew (*Tupaia glis*). *Brain Research* 124, 154–157.

Sherman, S.M. and Spear, P.D. (1982) Organization of visual pathways in normal and visually deprived cats. *Physiological Reviews* 62, 738-855.

Siegwart, J.T.J. and Norton, T.T. (1998) The susceptible period for deprivation-induced myopia in tree shrew. *Vision Research* 38, 3505-3515.

Siegwart, J.T.J. and Norton, T.T. (1999) Regulation of the mechanical properties of tree shrew sclera by the visual environment. *Vision Research* 39, 387–407.

Singer, W. (1982) Central core control of developmental plasticity in the kitten visual cortex: I. Diencephalic lesions. *Experimental Brain Research* 47, 209-222.

Sloper, J.J., Headon, M.P. and Powell, T.P. (1988) Experiments to study recovery of lateral geniculate nucleus cell size following monocular lid closure and reverse suture in infant monkeys. *Brain Research* 468, 47-59.

Smetters, D.K., Hahm, J. and Sur, M. (1994) An N-methyl-0-aspartate receptor antagonist does not prevent eye-specific segregation in the ferret retinogeniculate pathway. *Brain Research* 658, 168-178.

Smith, D.C., Holdefer, R.N. and Reeves, T.M. (1982) The visual field in monocularly deprived cats and its permanence. *Behavioural Brain Research* 5, 245-259.

Snider, C.J., Dehay, C., Berland, M., Kennedy, H. and Chalupa, L.M. (1999) Prenatal development of retinogeniculate axons in the macaque monkey during segregation of binocular inputs. *journal of Neuroscience* 19, 220-228.

Sorsby, A., Benjamin, B. and Sheridan, M. (1961) *Refraction and its components during the growth of the eye from the age of three.* Medical Council special report series, No. 301: Her Majesty's Stationery Office, London.

Spear, P.D. and Hou, V. (1990) Retinal ganglion-cell densities and soma sizes are unaffected by long-term monocular deprivation in the cat. *Brain Research.* 522, 354–358.

Spear, P.D. (1995) Plasticity following neonatal visual cortex damage in cats. *Canadian Journal of Physiology & Pharmacology* 73/1389-1397.

Spear, P.D. (1996) Neural plasticity after brain damage. *Progress in Brain Research* 108, 391–408.

Sprague, J.M. (1966) Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. *Science* 153, 1544-1547.

Stone, R.A., Lin, T., Iuvone, P.M. and Laties, A.M. (1990) Postnatal control of ocular growth: dopaminergic mechanisms. *Ciba Foundation Symposium* 155, 45–57.

Stryker, M.P., Sherk, H., Leventhal, A.G. and Hirsch, H.V. (1978) Physiological consequences for the cat's visual cortex of effectively restricting early visual experience with oriented contours. *journal of Neurophysiology* 41, 896909.

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

Sur, M., Humphrey, A.L. and Sherman, S.M. (1982) Monocular deprivation affects X- and Y-cell retinogeniculate terminations in cats. *Nature* **300,** 183–5.

Sur, M. (1993) Cortical specification: microcircuits, perceptual identity, and an overall perspective. *Perspectives on Developmental Neurobiology* **1,** 109–113,

Swindale, N.V. (1981) Absence of ocular dominance patches in dark-reared cats. *Nature* 290, 332–333.

Taylor, J.S. and Guillery, R.W. (1995) Effect of a very early monocular enucleation upon the development of the uncrossed retinofugal pathway in ferrets. *Journal of Comparative Neurology* **357,** 331–340.

Tessier-Lavigne, M. (1995) Eph receptor tyrosine kinases, axon repulsion, and the development of topographic maps. *Cell* 82, 345–348.

Tessier-Lavigne, M. and Goodman, C.S. (1996) The molecular biology of axon guidance. *Science* 274,1123–1133.

Thompson, I.D., Morgan, J.E. and Henderson, Z. (1993) The effects of monocular enucleation on ganglion cell number and terminal distribution in the ferret's retinal pathway. *European journal of Neuroscience* **5,** 357–367.

Thornberry, N.A. (1998) Caspases: key mediators of apoptosis. *Chemistry & Biology* **5,** R97–103.

Tieman, S.B. and Hirsch, H.V. (1982) Exposure to lines of only one orientation modifies dendritic morphology of cells in the visual cortex of the cat. *Journal of Comparative Neurology* **211**, 353–362.

Tieman, S.B. (1991) Morphological changes in the geniculocortical pathway associated with monocular deprivation. *Annals of the New York Academy of Sciences.* 627, 212–230.

Toldi, J., Joo, F., Feher, O. and Wolff, J.R. (1988) Modified distribution patterns of responses in rat visual cortex induced by monocular enucleation. *Neuroscience* 24, 59–66.

Toldi, J., Rojik, I. and Feher, O. (1994) Neonatal monocular enucleation-induced cross-modal effects observed in the cortex of adult rat. *Neuroscience* 62, 105–114.

Toldi, J., Feher, O. and Wolff, J.R. (1996) Neuronal plasticity induced by neonatal monocular (and binocular) enucleation. *Progress in Neurobiology* 48, 191–218.

Ton, C.C., Hirvonen, H., Miwa, H., Weil, M.M., Monaghan, P., Jordan, T., Van Heyningen, V., Hastie, N.D., Meijers-Heijboer, H., Drechsler, M. and *et al.* (1991) Positional cloning and characterization of a paired box- and homeobox-containing gene from the aniridia region. *Cell* 67,1059–74.

Tong, L., Spear, P.D., Kalil, R.E. and Callahan, E.C. (1982) Loss of retinal X-cells in cats with neonatal or adult visual cortex damage. *Science* **217**, 72–75.

Tong, L.L., Kalil, R.E. and Spear, P.D. (1991) Development of the projections from the dorsal lateral geniculate nucleus to the lateral suprasylvian visual area of cortex in the cat. *journal of Comparative Neurology* **314,** 526–533.

Trevelyan, A.J. and Thompson, I.D. (1992) Altered topography in the geniculo-cortical projection of the golden hampster following neonatal monocular enucleation. *European journal of Neuroscience,* 1104–1111.

Troilo, D., Gottlieb, M.D. and Wallman, J. (1987) Visual deprivation causes myopia in chicks with optic nerve section. *Current Eye Research* 6, 993–999.

Tron, E. (1929) The optical elements of the refractive power of the eye. *Graefes Arch Ophthalmology* 122, **1–33.**

Tychsen, L. and Burkhalter, A. (1995) Neuroanatomic abnormalities of primary visual cortex in macaque monkeys with infantile esotropia: preliminary results. *journal of Pediatric Ophthalmology & Strabismus* 32, 323–328.

Uhl, F., Franzen, P., Lindinger, G., Lang, W. and Deecke, L. (1991) On the functionality of the visually deprived occipital cortex in early blind persons. *Neuroscience Letters* 124, 256–259.

Uhl, F., Franzen, P., Podreka, I., Steiner, M. and Deecke, L. (1993) Increased regional cerebral blood flow in inferior occipital cortex and cerebellum of early blind humans. *Neuroscience Letters* **150,** 162–164.

Van Sluyters, R.C. and Levitt, F.B. (1980) Experimental strabismus in the kitten. *Journal of Neurophysiology* 43, 686–699.

Vizuete, M.L., de la Roza, C., Steffen, V., Machado, A. and Cano, J. (1993) Changes in neurotransmitters in superior colliculus after neonatal enucleation: biochemical and immunocytochemical studies. *Neuroscience* **56,** 165–176.

Von Noorden, G.K. and Dowling, J.E. (1970) Experimental amblyopia in monkeys. II. Behavioral studies in strabismic amblyopia. *Archives of Ophthalmology* 84, 215–220.

Von Noorden, G.K. (1978) Application of basic research data to clinical amblyopia. *Ophthalmology* 85, 496–504.

Wakabayashi, S., Freed, L.M., Bell, J.M. and Rapoport, S.I. (1994) *In vivo* cerebral incorporation of radiolabeled fatty acids after acute unilateral orbital enucleation in adult hooded Long-Evans rats. *Journal of Cerebral Blood Flow & Metabolism* 14, 312–323.

Wallman, J., Turkel, J. and Trachtman, J. (1978) Extreme myopia produced by modest change in early visual experience. *Science* 201, 1249–1251.

Wallman, J., Gottlieb, M.D., Rajaram, V. and Fugate-Wentzek, L.A. (1987) Local retinal regions control local eye growth and myopia. *Science* 237, 73–77.

Wallman, J. (1990) Myopia and the control of eye growth. Introduction. *Ciba Foundation Symposium* 155, 1–4.

Wallman, J. (1990) Retinal influences on sclera underlie visual deprivation myopia. *Ciba Foundation Symposium* 155, 126–134.

Watkins, D.W., Wilson, J.R. and Sherman, S.M. (1978) Receptive-field properties of neurons in binocular and monocular segments of striate cortex in cats raised with binocular lid suture. *Journal of Neurophysiology* 41, 322–337.

Weliky, M. and Katz, L.C. (1999) Correlational structure of spontaneous neuronal activity in the developing lateral geniculate nucleus in vivo. *Science* 285, 599–604.

Weller, R.E., Kaas, J.H. and Ward, J. (1981) Preservation of retinal ganglion cells and normal patterns of retinogeniculate projections in prosimian primates with long-term ablations of striate cortex. *Investigative Ophthalmology & Visual Science* **20,** 139–148.

Wiesel, T.N. and Hubel, D.H. (1963) Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *J. Neurophysiol* **26**, 978–993.

Wiesel, T.N. and Raviola, E. (1977) Myopia and eye enlargement after neonatal lid fusion in monkeys. *Nature 266,* 66–68.

Wildsoet, C. and Wallman, J. (1995) Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. *Vision Research* **35,** 1175–1194.

Will, B. and Kelche, C. (1992) *Environmental approaches to recovery of function from brain damage: A review of animal studies (1981–1991),* New York and London: Plenum Press.

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 Research* 136, 277–287.

Wong, R.O., Meister, M. and Shatz, C.J. (1993) Transient period of correlated bursting activity during development of the mammalian retina. *Neuron* 11, 923–938.

Xu, P.X., Zhang, X., Heaney, S., Yoon, A., Michelson, A.M. and Maas, R.L. (1999) Regulation of Pax6 expression is conserved between mice and flies, *Development* 126,383–395.

Zeki, S. (1993) *A Vision of the Brain,* Oxford, England: Blackwell Scientific Publications.

Zilles, K., Wree, A., Petrovic-Minic, B., Schleicher, A. and Beck, T. (1989) Different metabolic changes in the lateral geniculate nucleus and the superior colliculus of adult rats after simultaneous or delayed double enucleation. *Brain Research* 488, 14–21.