Visual System Development and Neural Activity

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GLOSSARY

amblyopia The impairment of vision without detectable organic lesion of the eye.

ectopic Positioned abnormally within the body.

neurotrophic factor A molecule, usually a protein, that will facilitate the growth or repair of nerve cells.

ocular dominance column An area in the visual cortex that receives input predominantly from one eye.

transcription factor A protein required for recognition by RNA polymerases of specific stimulatory sequences in eukaryotic genes.

visuotopy The arrangement of cells and the connections between neural structures such that they maintain a topographic representation of the visual field.

Neural structures are specified very early when the future nervous system is still a sheet of cells referred to as the neural plate and before this sheet folds to form the neural tube. These early steps involve evolutionarily conserved inductive signaling pathways that initially establish regional identity. Subsequently, at the time when cells undergo their final cell division, the cells within different regions of the visual system become committed to their specific fates or individual identities. Evidence from studies in a variety of animals suggests that molecular gradients, timing of axon arrival, and correlated spontaneous activity all help to shape early targeting decisions and to establish precise connections. Refinements of the system involve active growth and branching of axons and dendrites, formation of synapses, and elimination of cells, axon collaterals, and some synapses. Further refinements of visual system development depend on activity and competition for limited supplies of neurotrophic factors but do not necessarily require visual experience. However, visual experience, especially during critical periods of active growth, can dramatically modify the final outcome.

I. INTRODUCTION

Mammalian development is an elegant process by which a single cell becomes a complete organism containing multiple organ systems that are highly interconnected. This is never more evident than during neural development. A central issue in the study of neurobiology concerns not only how nerve cells become connected in the first place but also how those connections become organized in such a way that the sensory world is represented. The topographical specificity of different parts of the mammalian visual system is dependent on highly ordered connections. Consider that the mammalian brain contains at least 100 billion neurons and that each of these

neurons can make more than 1000 specific connections with other neurons. Specificity is particularly evident in the visual system, in which a topographic map of visual space is maintained throughout each level of visual processing. For example, in the macaque monkey, a modest estimate of the number of visual areas requires that at least 30 visuotopic maps connect correctly in the developing brain; in humans there may be even more visual areas. Each cell within one of these maps processes information from a specific zone of the visual world, and that cell's neighbor processes information from an adjacent zone and so forth. Neighboring cells connect with neighboring cells in other visual areas. This characteristic is called visuotopy.

One approach that may be useful in elucidating the complex wiring of the mammalian visual system is to assume that axons make connections through a sequence of simpler evolutionarily conserved mechanisms. In mammals, research suggests that the earliest stages in the development of the nervous system are similar across a range of diverse species and involve similar if not identical molecular pathways. The similarities in these early steps of neural development imply the existence of powerful constraints on the regulatory relationships between genes that control early phenotypes (e.g., the characteristics and appearance of different parts of the nervous system). Good examples of these relationships come from genetic studies of eye and head development in flies (*Drosophila*), mice, and humans. In mice and humans the paired box *pax*-6/*aniridia* gene and its homolog in flies, the eyeless gene, play major roles in eye and craniofacial development. These genes control transcription factors that regulate a cascade of other genes important for eye and head formation. When loss-of-function mutations are produced in the eyeless gene, flies develop with no eyes, very reduced eyes, or defective eyes. Similar phenotypes are seen with genetic mutations in the *pax*-6/*aniridia* gene in mice and humans. Astoundingly, ectopic expression of either the fly eyeless gene or the pax *6* gene results in the development of fully formed insect eyes on parts of the mutant fly's body that do not normally have eyes, such as the leg or wing. These remarkable results not only argue for a common evolutionary origin of eye development, but also reinforce the view that the earliest developmental programs are governed by highly conserved rules.

Although it is not the purpose of this article to focus on these early steps in development, the previous example has relevance. Later steps in neural development, in general, and visual system development, in particular, also involve evolutionarily conserved mechanisms. Since flies, mice, and humans differ in organization, size, and complexity of the brain, it is obvious that there must be developmental differences. Nevertheless, dramatic differences in adult brain organization can involve small changes in basic developmental mechanisms, such as changes in the number of cell divisions that occur before founder populations stop dividing, or changes in the number of cells that are eliminated during the periods of cell death that occur as a part of normal development in all nervous systems. The role of other mechanisms such as neural activity may be more important to the development of connections in large, complex nervous systems, although the basic mechanisms that translate that activity into cell growth or the formation of synaptic connections between nerve cells are also conserved across species.

In this article, we limit our consideration of development to two interconnected and well-studied visual centers in the brain, the lateral geniculate nucleus (LGN) in the thalamus and the primary visual cortex or V1 (Fig. 1). First, we provide an overview of the development of these visual areas in the larger context of brain development and discuss how these structures take on their adult shape. Then, we show how specialized laminar patterns and topographic connections between these structures can develop according to molecular cues. Finally, we explore possible mechanisms for the establishment of specificity, including the role of neural activity in forming and maintaining connections.

II. OVERVIEW OF VISUAL SYSTEM DEVELOPMENT

A. Early Neural Development

The brain begins as a simple plate of progenitor cells that eventually forms a tube that bends and balloons out into three fluid-filled vesicles during the process of development. Even before the neural plate forms a tube, however, communication takes place between cells that determines which progenitor or founder cells will give rise to specific broad regions of the visual system, including regions that contain the retina, the LGN, and the visual cortex (Fig. 2). An enormous array of transcription factors and extracellular molecular signals have been identified that are involved in

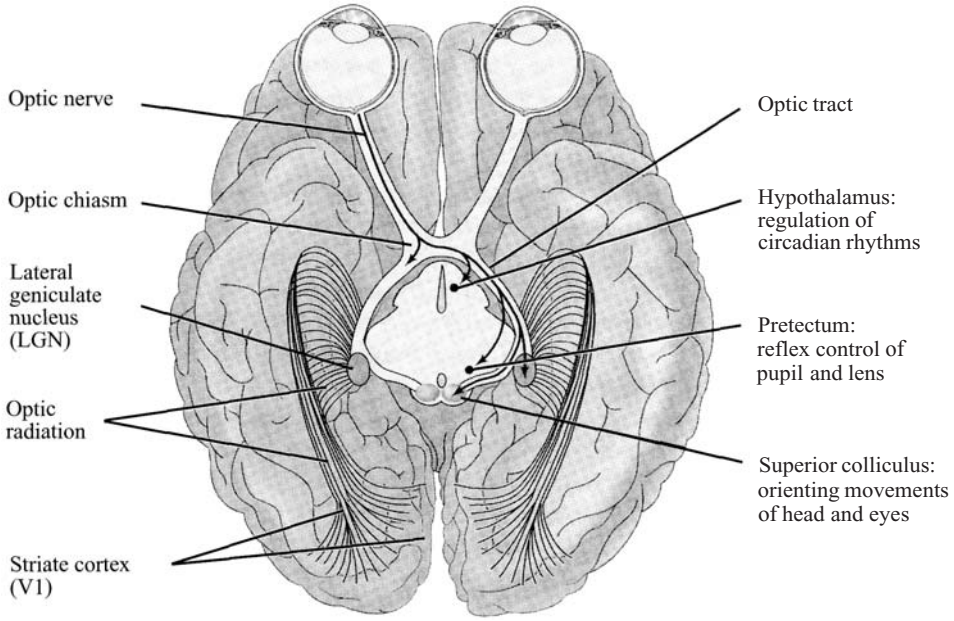

Figure 1 The visual pathways shown as a schematic viewed from the ventral surface of the human brain. The axons from ganglion cells located in the retina leave the eyes as the optic nerve. The ganglion cells located in the temporal retina (shown for the right eye) send axons to the same side (ipsilateral) of the brain (arrow), whereas the axons in the nasal retina cross at the optic chiasm to the other hemisphere or contralateral side of the brain. Once the axons have left the optic chiasm they bundle together as the optic tract. Groups of axons leave the optic tract at various points to make synapses with groups of cells (nuclei) conserved with different visual functions, such as the hypothalamus (circadian rhythms), the lateral geniculate nucleus (LGN); (conscious vision), pretectum (pupillary and lens reflexes), and superior colliculus (orienting head and eyes). The superior colliculus is homologous with the optic tectum of nonmammalian vertebrates. Cells in the LGN send axons to the primary visual cortex or striate cortex, also called V1, located at the back of the brain in the occipital lobe [reproduced with permission from Purves, D., *et al.* (Eds) (1997). *Neuroscience.* Sinauer, Sunderland, **MA].**

these early stages of regional specification. 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 the expression of a number of genes; however, specific molecules that define the exact boundaries of the developing LGN or primary visual cortex have not been identified.

As development progresses, cells divide close to the inner (ventricular) surface of the neural tube. Initially, all cells extend their processes across the full width of the neural tube, but later only a subset of cells, the radial glial cells, span the full width of the developing forebrain. Radial glia are used by other cells as migratory railway guides to move from the ventricular zone to their final destinations, whether in the developing LGN or visual cortex. Each neural progenitor cell, or stem cell, undergoes a certain number of cell divisions in the young animal, until it divides no more in the adult. This final mitotic division is termed the birth date of the neuron. After the final cell division a neuron differentiates or matures. Neurons in different areas of the brain, such as the LGN and visual cortex, exhibit differences, reflecting their variable differentiation programs. Cells within different neural structures mature at different times in the developmental process and at different rates. Additionally, each neural structure may have its own gradient of development, such that some cells in the nucleus mature before others. Finally, as neural structures mature many developing neurons are eliminated through cell death. This natural cell death process not only eliminates cells with incorrect connections but also allows the production of transient cell populations that help to shape the structures and connections of the nervous system by providing temporary scaffolding for migrating neurons and guideposts for developing axons. The development of the mammalian brain is a highly dynamic process involving multiple overlapping gradients of progression. Cells in the brain experience multiple combinatorial genetic and activity-dependent cues at different times in their development that ultimately produce the complex structure of the adult mammalian brain.

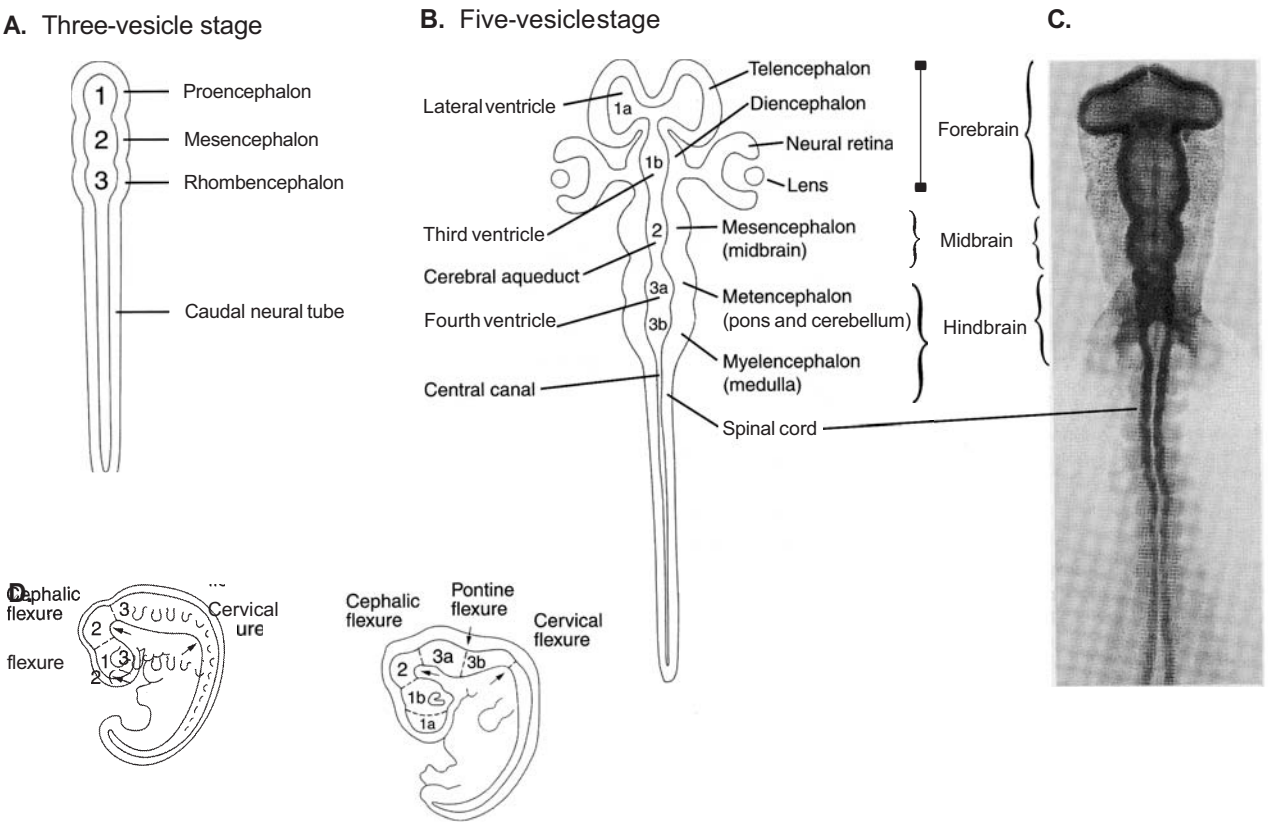

Figure 2 Successive stages of development of the neural tube. The nervous system begins as a plate of tissue (not shown) that rolls up to form a tube. **(A)** Three-vesicle stage. At early stages of development only three brain vesicles are present. (B) Five-vesicle stage. At later stages, two additional vesicles form, one in the area of the forebrain (1a and 1b) and the other in the hindbrain (3a and 3b). Before the neural tube forms, cells are prespecified such that the retina and lateral geniculate nucleus will form from part of the diencephalon (3b), the visual cortex from the telencephalon (1a), and the superior colliculus from the midbrain (2). (C) Micrograph showing a dorsal view of the neural tube at an early stage of development. The expansion of the future telencephalic vesicle is apparent (micrograph of the chick neural tube provided by G. Schoenwolf). (D) The positions of the cephalic, pontine, and cervical flexures [from Kandel, E. R., Schwartz, J. H., and Jessell, T. **M.** (Eds.) (2000). *Principles of Neural Science,* 4th ed. Reproduced McGraw-Hill Companies, with permission of the New York].

B. Development of LGN Structure

The adult LGN of many mammals, including humans, is laminated with compartmentalized input. Each LGN layer receives input from only one eye. Each layer also contains a topographic map of one-half of the visual world. The LGN layers are stacked on top of each other like a set of pancakes (Fig. **3).** In primates there is layer specialization such that small, medium, and large cells are segregated into different layers and carry different types of visual messages to primary visual cortex. During development, the future large LGN cells are born and begin migrating from the ventricular surface toward their final destination before the future smaller LGN cells. The differing extracellular environment encountered by LGN cells born at different times during development may change the genetic program of those cells, such that the different classes of cells adopt different morphological and neurochemical identities during differentiation. In fact, in visual cortex there is evidence supporting the view that important decisions about cell fate are made at the time progenitor cells divide in the ventricular zone. It is likely that the same rules apply to cells throughout the developing neural tube. During development, LGN progenitor neurons destined to represent central vision versus peripheral vision divide and mature in a gradient such that cells that will carry information about the central visual world develop earlier than cells that will carry information from the visual periphery. Gradients in the timing of cell birth and maturation of LGN

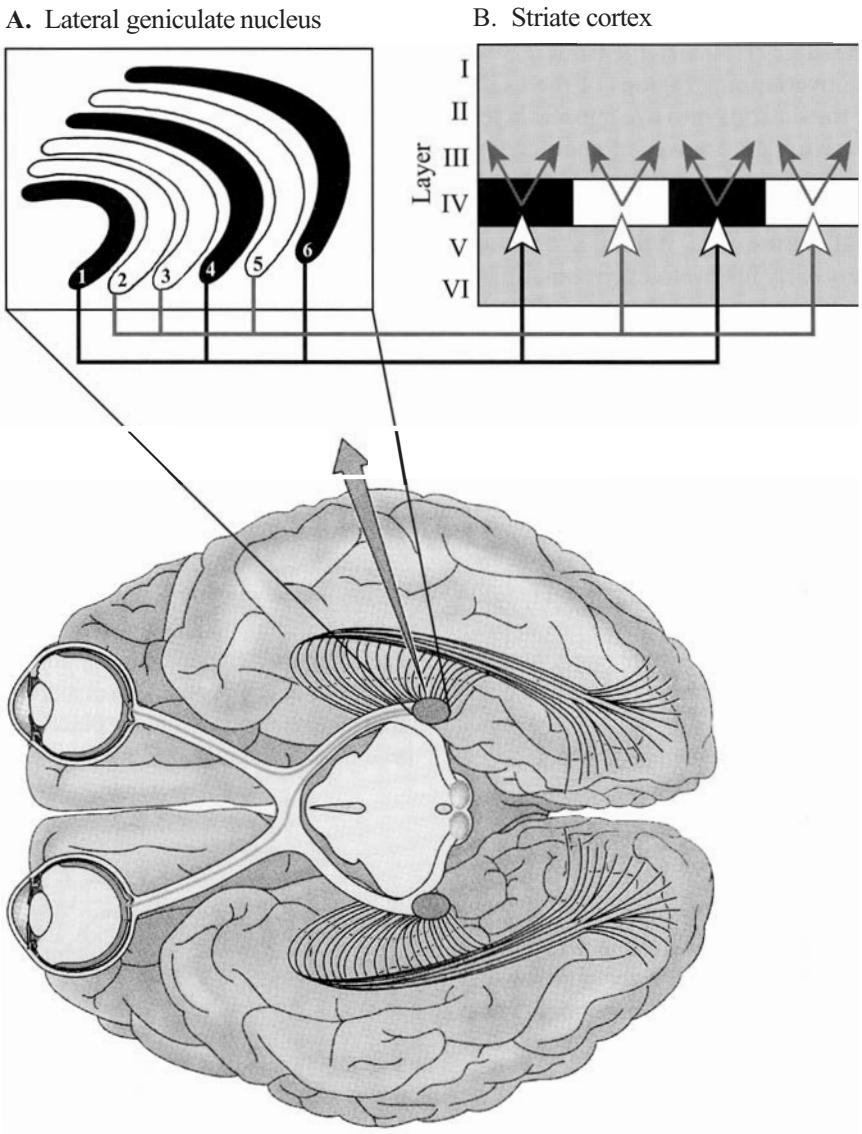

Figure 3 The connections between the lateral geniculate nucleus (LGN) and striate cortex (primary visual cortex). The visual pathway is shown as a schematic viewed from the ventral surface of the human brain. This same view is also shown in Fig. 1. Although the LGN receives inputs from both eyes, these are segregated in separate layers as shown in **(A)** The first two layers contain large cells (magnocellular layers), and the remaining four layers (parvocellular cells) contain medium-sized cells. Not shown are the small cell (koniocellar) layers that lie between each of the main layers shown. (B) In many species, and most primates, the inputs from the two eyes remain segregated in ocular dominance columns of layer IV, the primary target of LGN axons. Layer IV neurons send their axons to other cortical layers; it is at this stage that information from the two eyes converges onto individual neurons [reproduced with permission from Purves, D., *et al.,* (Eds) (1997). *Neuroscience.* Sinauer, Sunderland, MA].

progenitors and within any structures connected to the LGN (such as the eye and the primary visual cortex) may be one of several simple mechanisms that ensure that topographically correspondent regions connect properly.

The retina and the visual cortex, the main inputs to the LGN, both innervate the LGN visuotopically. There is evidence that axons leaving visual cortex and retina grow out very early but may not reach their targets at the same time. In monkeys, retinal ganglion cell axons of different classes grow to the LGN very early and terminate immediately within the appropriate portions of the LGN, demonstrating that some retinal axons are molecularly specified to connect to

specific LGN target regions. However, retinal ganglion cell axons of the same class, arriving from the two eyes initially invade overlapping regions of the LGN. The segregation of these axons into eye-specific layers seems to depend on correlated waves of spontaneous activity in the retina since blocking such activity blocks the normal segregation of retinal axons, at least in carnivores. Cortical axons, like retinal axons, approach the LGN very early in development but, unlike retinal axons, do not invade the nucleus immediately. A special early-born class of cortical cells, the cortical subplate cells, may be the first to send axons to the thalamus. These cells may pioneer the later-born layer VI cell axons that will form permanent connections with the LGN; however, the pioneer axons must still find their way to the LGN. Evidence suggests that the earliest axons use a variety of membrane-bound cues to locate correct targets. When cortical axons do invade the LGN, they immediately grow into visuotopically correct areas of the nucleus and do not appear to require a sorting period, although some smaller refinements may take place as these axons mature.

C. Development of Visual Cortical Structure

Multiple cortical areas, defined by morphology, physiology, and connections with other cortical and subcortical nuclei, make up the neocortex, like a patchwork quilt. One patch of the quilt is the primary visual cortex, located in posterior or occipital cortex. The adult visual cortex contains a precise topographic map and, like all of mammalian cortex, is laminated. The neocortex has six layers. Axons arriving from the LGN synapse primarily in layer IV of visual cortex. In primates, axons from LGN cells of different functional classes (e.g., large versus small LGN cells) synapse in different divisions of cortical layer IV or in distinct compartments located above layer IV. Additionally, LGN cells representing the left and right eye send axons to separate columns of cortex such that cells in a particular column of cortex respond to a stimulus to one eye or the other preferentially (Fig. 3). Cells in layer IV make connections with layers above and below layer IV, and this is where the fusion of information from the two eyes occurs. Cortical cells in layer VI send axons back to the LGN. Also, each ocular dominance column is divided into smaller columns in which cells respond to one orientation of a bar of light. Orientation columns are arranged mainly in pinwheels, such that all orientations are roughly represented within each ocular dominance domain and visuotopy is maintained across columns (Fig. 4). The aforementioned scenario is more simplistic than the biological situation but serves to emphasize some of the complexities of organization that must be achieved during development for the visual cortex to function properly.

As does the developing LGN, the developing cortex begins as a simple epithelium—a thin columnar sheet of cells. As development advances and cells divide, this sheet of cells becomes thicker. The radial glial cells maintain contact with both the ventricular and the pial sides of this sheet, whereas cortical neuroblasts begin dividing at the ventricular zone. Soon, three precortical subdivisions can be recognized. The ventricular zone is the most ventral, where excitatory cortical cells are born from a resident stem cell pool. Interestingly, inhibitory cortical cells, like olfactory bulb cells, may originate from a noncortical stem cell population located in the ganglionic eminence (e.g., the developing basal ganglia). Above the ventricular zone is the intermediate zone, a highway for axons, where corticofugal and corticopetal axons are located. Above the intermediate zone is the preplate, a layer of early born cells that have migrated along radial glial fibers to lie

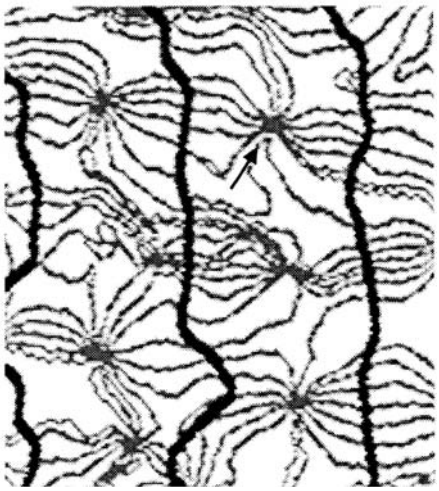

Figure 4 Orientation columns in the visual cortex of the monkey. Comparison of optical image maps of orientation preference and ocular dominance in monkey visual cortex. The thick black lines represent the borders between ocular dominance columns. The thin gray lines represent isoorientation contours, which converge at orientation pinwheel centers (arrow). Each left and right eye ocular dominance column represents a common region of visual space. An adjacent set of columns represents an adjacent region of visual space and so forth across the visual cortex [adapted with permission from Obermeyer, K., and Blasdel, G. G. (1993). Geometry of orientation and ocular dominance columns in monkey striate cortex. *J. Neurosci.* **13,** 114–129].

adjacent to the pial surface. **As** cell division proceeds, the preplate is split by migrating cells to form the marginal zone (the future layer I of cortex) dorsally and the subplate ventrally. Cells that will form the remaining adult cortical layers will migrate to lie between the marginal zone and subplate. Most of the cells within the preplate and subplate subsequently die. Unlike the LGN, in which cells that are born first lie closest to the pial surface of the neural tube, cortical layers II–VI are formed in an inside–out gradient such that cells born early become the lower layers, whereas cells born later migrate through these layers to form the upper layers (Fig. *5).* The transitory layers formed from the original preplate are very important for the proper formation of the other layers of cortex. If the marginal zone is disrupted or not formed, then the cortical layers will not develop in the proper order. For instance, in the reeler mouse, a mutant mouse lacking the gene *reelin* (normally expressed by cells in the marginal zone), the cortical layers develop upside-down or in an outside–in gradient. If the subplate is experimentally removed, the cortical layers develop normally, but axons from the developing LGN are unable to find their proper cortical target.

How the many functionally distinct areas of the neocortex (e.g., the patches of the quilt) differentiate within the forebrain is less well understood. Evidence indicates that parcelation of the forebrain into subdivisions such as the visual cortex involves the expression of a cascade of regulatory genes that first subdivide broad regions of the forebrain and subsequently interact to regulate functionally specific areas. **As** mentioned previously, in the hindbrain, sequential bands have been identified that differentially express certain genes. These segmental regions are termed rhombomeres and are thought to represent early specification of nuclei in different segments of the brain stem. Some candidates for mediating interactions across brain stem boundaries are members of the Ephrin (Eph) receptor tyrosine kinase family. It is noteworthy that mutant mice lacking connections between the thalamus and cortex still show differential regional expression of genes across the neocortex as well as the normal development of cortical layers independent of this extrinsic input. Nevertheless, there is considerable evidence that extrinsic inputs from the thalamus, particularly those that bring sensory information about the outside world such as visual signals from the retina, can radically alter the pattern of development of cortical areas.

III. AXON PATHFINDING: WIRING THE LGN AND VISUAL CORTEX

A. Molecular Cues

A persistent mystery in developmental neuroscience is how axons travel great distances to find their way to highly specific targets. Correct target selection and the refinements involved in the formation of visuotopic connections between the retina, LGN, and cortex involve both genetic and epigenetic cues. Examples of

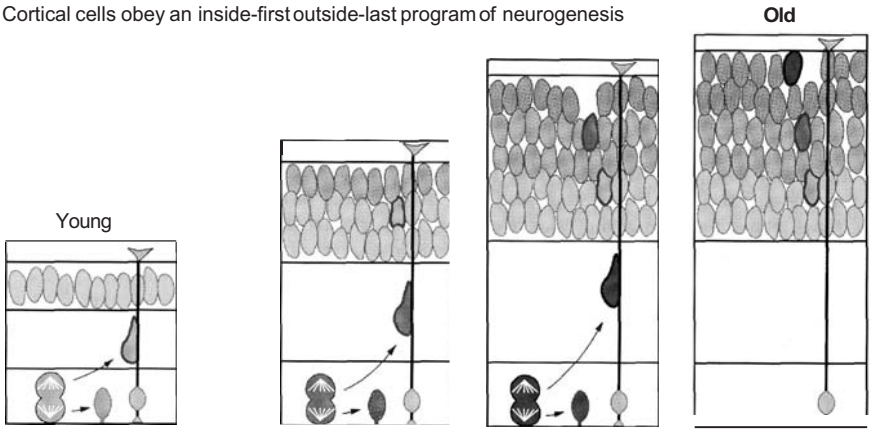

Figure 5 Generation and migration of neurons in the mammalian cerebral cortex. Cortical neurons are generated in an inside-first, outside-last order. Neurons born within the ventricular zone at the early stage migrate to the deepest layers of the cortical plate. Neurons generated at later stages migrate past the earlier generated neurons to form the more superficial layers of the cortex [adapted with permission from McConnel, **S.** K. (1992). The determinants of neuronal identity in the mammalian cerebral cortex. In *Determinants of Neuronal Identity* (M. Shantiland, and E. Macegno, Eds.), pp. 391–432. Academic Press, New York].

genetic mechanisms include the presence of membrane-bound and secreted molecules, which are permissive, instructive, or obstructive cues for axons with the proper receptors. Axons can grow on various substrates in the brain, including the extracellular matrix, other neural cell membranes, and glial cell membranes (such as the radial glia on which LGN and cortical cells migrate). Developing axons have a specialized structure, a growth cone, at their tip to help them navigate through the extracellular milieu (Fig. 6). This highly motile structure contains receptors capable of transmuting signals about the local environment. The growth cone guides the axon along pathways toward the target region defined by a combination of positive or negative cues.

Once an axon reaches its target, it often will send out a simple T-shaped branch as shown for the LGN axon growing into visual cortex in Fig. 7. Within the visual system, axons often reach their target region while the target cells are still migrating into position or just after migration is complete. Growth cones on the tip of axon branches can detect gradients of membrane-bound molecules to guide axons to their general addresses within a target structure. Axons respond differentially to these molecular gradients within the target based on their initial specification that likely occurred at the time of final cell division and prior to axon outgrowth.

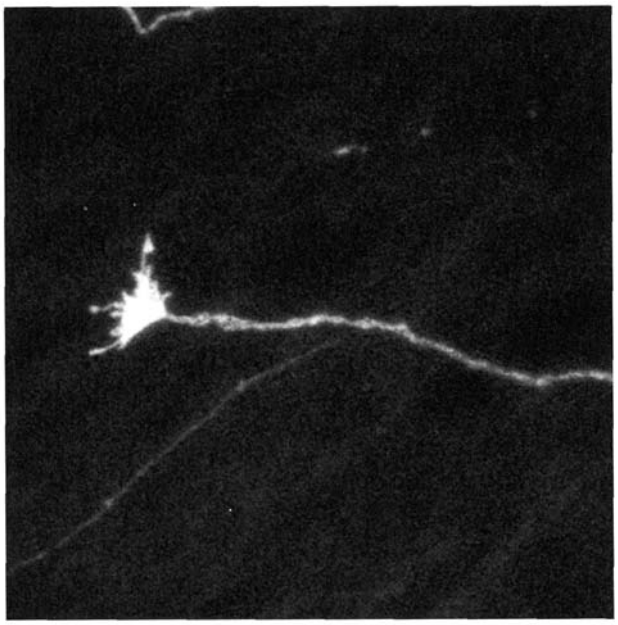

Figure 6 An example of a thalamocortical axon with a growth cone in neonatal mouse brain. The growth cone is a complex, dynamic structure at the tip of the growing axon that samples the local environment, guiding the axon to its target.

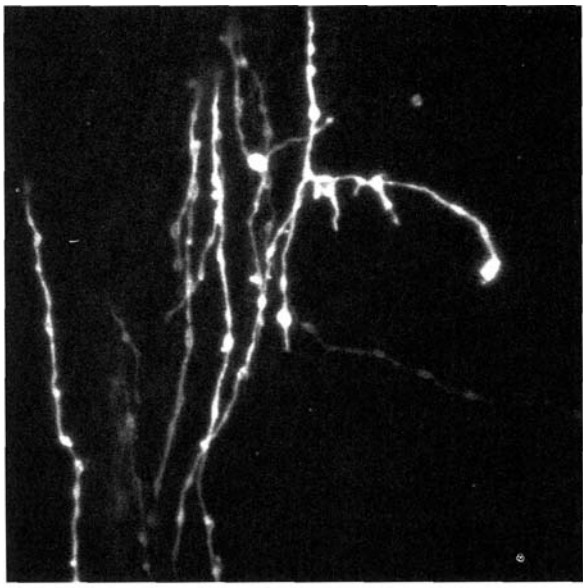

Figure 7 Thalamocortical axons initially exhibit collateral T-shaped side branches when they begin to innervate the cortical plate as shown here from the neocortex of a mouse on the day of birth.

Retinal ganglion cell axons from different retinal locales will therefore respond differently to cues at the target based on their unique growth cone receptors. As mentioned previously, a good example of this process involves the specificity with which different retinal ganglion cell classes target regions of the LGN. Although many molecules have been identified that may guide retinal ganglion cell axons to the right targets, evidence has converged on two membrane-bound ligands of the receptor tyrosine kinases, ephrin A2 and ephrin A5. Both of these ligands are expressed in gradients in the optic tectum, another brain area innervated by retinal ganglion cells. Eph kinases are distributed in gradients in the retina. These two molecular gradients may regulate retinotectal and retinogeniculate topography because ephrins bind to Eph kinases and activation of Eph kinases inhibits axon outgrowth. In particular, the levels of ephrin A2 and A5 are higher in the posterior tectum than in the anterior tectum, and this could inhibit growth of temporal retinal axons, which are rich in the appropriate Eph kinases (Fig. 8). Moreover, retinal axons in mice with mutations in ephrin A2 and A5 exhibit a loss of visuotopy and innervate areas of the optic tectum that they normally would avoid. Interestingly, members of this same family of ephrin molecules are implicated as cues for establishing the proper laminar connections in visual cortex. Therefore, members of the ephrin family may be involved in early regional

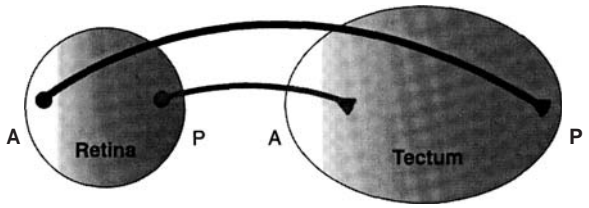

Figure 8 Eph kinases are distributed in gradients in the retina, and ephrins are distributed in gradients in the optic tectum. These two molecular gradients may regulate retinotectal visuotopy because ephrins bind to eph kinases and activation of eph kinases inhibits axon outgrowth.

differentiation in the brain, as well as the establishment of axonal connections later. This example illustrates how a single family of similar molecules can direct several very different developmental programs, sometimes simultaneously, in different neural regions and with overlapping expression patterns, and it underscores the high level of conservation of mechanisms in neural development.

B. The Role of Activity

As neurons mature, they begin to display electrical activity. Neural activity has been shown to play an important role in the correct targeting of axonal connections as well as the formation and maintenance of synapses. The role of neural activity in shaping connections is not restricted to the postnatal period when animals begin to use their senses to explore their environment. Neurons are active well before birth, especially in animals such as primates that are born at a relatively mature developmental stage. Experiments in cats and ferrets have demonstrated that prior to visually driven activity (at a time when the eyelids are still closed), correlated waves of spontaneous activity already exist in the retina and brain. Neurons at this stage are coupled by developmentally transient gap junctions (at least in the retina and the visual cortex, but probably also within other areas of the visual system). The waves of spontaneous activity appear to be important to the segregation of left and right eye inputs within the developing LGN layers and to the segregation of eye-specific inputs into ocular dominance columns in cortex. As mentioned earlier, blocking this activity in prenatal cats and postnatal ferrets disrupts the binocular segregation process. In the examples cited previously, activity likely affects the construction of new axonal branches and synapses and not the retraction of inappropriate connections since the manipulations are initiated when retinal and geniculocortical axons still have a simple stick-like morphology.

During the period of activity-dependent modification of connections, many manipulations are made to the visual system in an effort to define the mechanisms that relate activity to the growth of neural processes and to synaptogenesis. The most famous of these experiments were done in the 1960s by David Hubel and Torsten Wiesel, who showed that preventing one eye of a kitten from seeing during early life resulted in a number of dramatic changes in the connections and function of the visual system. In their experiments, they sutured the lid of one eye closed, but it is now known that the same effects are obtained as long as useful pattern vision is prevented; the amount of light reaching the retina is not as important. In these experiments, they found that kittens could no longer see well out of the deprived eye (i.e., they developed amblyopia) if the deprivation continued past 3 months of age. These investigators also found that geniculocortical axons from the deprived eye occupied less territory in layer IV of visual cortex (the deprived ocular dominance column was smaller) and cells in the cortex now responded mainly to the normal eye. If the kittens were allowed to develop normally for the first 3 months of age, monocular lid suture would no longer affect ocular dominance columns, suggesting that there is a window of time or critical period during which visual experience can have an impact on ocular dominance column formation. If the eye was sutured and shortly afterwards opened again during the critical period, then normal ocular dominance formation would occur. The effects of monocular deprivation are not the consequences of disuse, as Hubel and Wiesel clearly demonstrated, since depriving both eyes of useful pattern vision has much milder effects on the visual system (Fig. 9).

These experiments, along with numerous experiments that followed, suggest that developing geniculocortical axons that receive input from the left and right eyes can compete with one another for territory in cortex. The working hypothesis is that appropriate levels of activity and the temporal correlation of that activity in potential pre- and postsynaptic partners provide axons access to appropriate levels of growth factors (i.e., neurotrophins). These neurotrophins, in turn, activate the cellular machinery that allows axons to grow and develop synapses (Fig. 10). Axon growth is clearly constrained by many other factors in the target tissue discussed earlier, including factors that directly repel or attract axons or substrates that

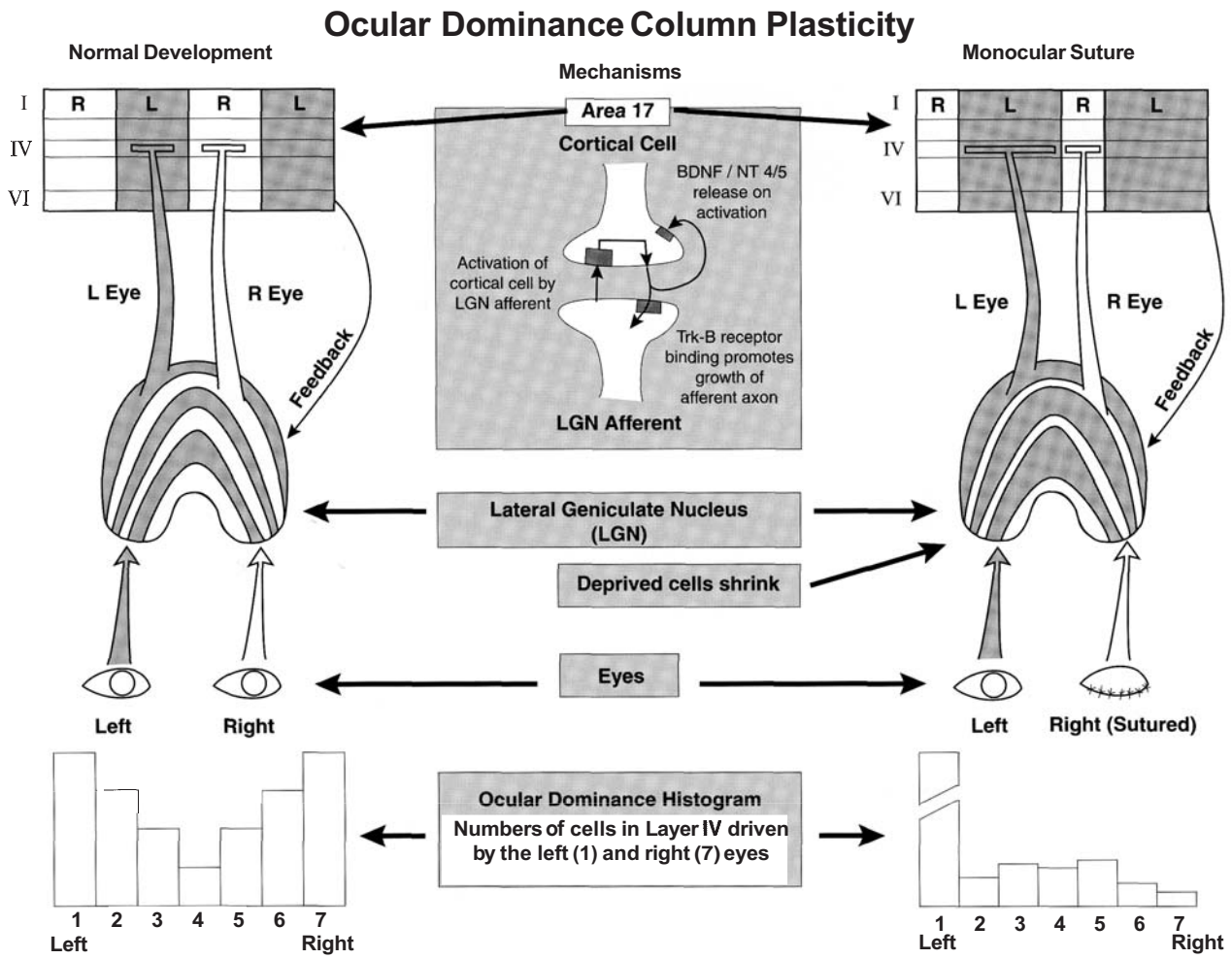

Figure 9 Changes within the LGN and visual cortex (area 17) seen following monocular lid suture in a macaque monkey. Axons from the left and right eyes segregate into six layers within the LGN early in development. LGN axons segregate into ocular dominance columns within layer IV of area 17. Axon segregation within the LGN and cortex takes 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 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 nondeprived 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) eyes compete within cortex for limited quantities of neurotrophic factors. Evidence suggests that the neurotrophins, brain-derived neurotrophic factor (BDNF) or neurotrophin (NT) 4/5, are involved, as shown in the center. 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 [adapted with permission from Barker, R. **A.,** and Barasi, **S.,** (with Neal, M. J.) (1999). *Neuroscience at a Glance* Blackwell Science, Oxford].

support growth. In addition, it is evident that pattern vision per se is not essential for setting up ocular dominance columns in the first place since monkeys are born with well-developed ocular dominance columns. Nevertheless, basic cellular mechanisms that normally help axons driven by the left and right eyes to segregate into layers in the LGN and into columns in the cortex are likely the same as those that allow for plastic changes following manipulations of visually driven activity.

How does activity help some developing axons to grow processes or form or strengthen some synapses at the expense of others? **A** working model for this process was originally derived from the learning model

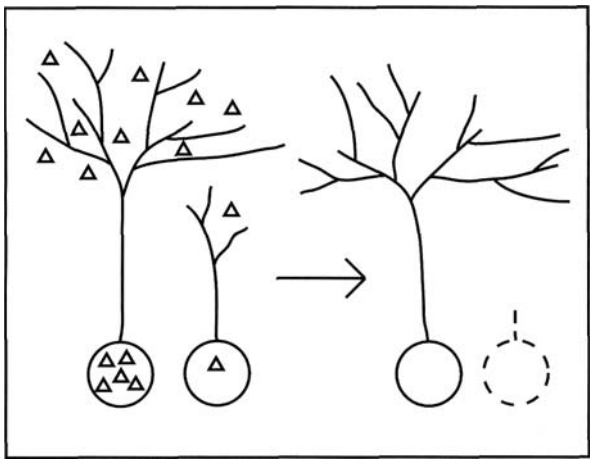

Figure 10 Selective access to growth factors can influence the survival of neurons. Neurons (circles) compete for a limited supply of growth factors (triangles). Neurons that do not get enough of the growth factor may die or have smaller axonal trees.

of Donald Hebb (1949). Hebb proposed that pathways that are active together form or strengthen connections at the expense of those that are inactive or not co-active (Fig. 11). In Hebb's model each instance of coactivation in an assembly of connected cells strengthens these connections. The favored synapses eventually become so strong that memories form. Hebb's idea for the strengthening of synapses in learning and memory provides a good model to explain how activity can influence the development of initial connections.

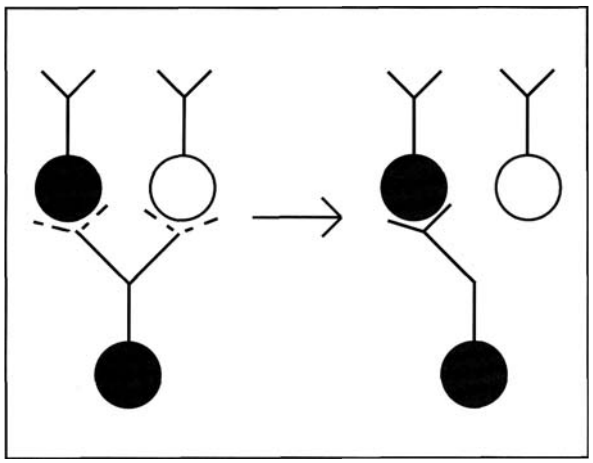

Figure 11 A simple schematic depicting Hebbian mechanisms of axonal plasticity. The two black cells on the left have synchronous action potentials. The white cell does not fire coincidently with the black cells. Initially, the lower black cell sends a synapse to both upper cells (dashed lines). After a certain amount of time, the synapse between the black cells is strengthened, whereas the synapse between the black and white cells is weakened or eliminated.

Hebb's hypothesis can be used to explain the development of ocular dominance columns if sets of correlated inputs tend to exclude uncorrelated inputs and are additionally constrained by molecular gradients related to retinotopy. Support for this idea was best demonstrated in cases in which an extra eye was transplanted to the head of a developing frog (Fig. 12). In frogs, each eye normally sends a crossed projection to each optic tectum. When a third eye is introduced, two eyes divide one tectal territory by developing ocular dominance bands in the dually innervated tectum as would be predicted by the model.

At the cellular level in mammals, the working model that has been proposed to explain how correlated activity can influence the formation and strengthening of synapses and the growth of neural processes involves a special class of receptors for the transmitter glutamate, the *N*-methyl-D-aspartate (NMDA) class of glutamate receptors. The NMDA receptors bind the transmitter glutamate, but such binding has no effect unless another condition is satisfied. At the "resting" membrane potential, the NMDA receptor's channel is blocked by magnesium. Strong depolarization of the postsynaptic membrane removes the magnesium block by electrostatic repulsion. If glutamate now binds to the NMDA receptor while the cell is depolarized, calcium is able to enter the cell via the NMDA channel. Calcium ions that enter through the NMDA channel activate kinases in the cell. Through either kinase activation or some other calcium-dependent series of steps, the postsynaptic cell is modified and potentially more sensitive to transmitter release. Additionally, a retrograde molecular signal or neurotropin (e.g., neurotrophin 4/5 or brain-derived neurotrophic factor) may be released from the postsynaptic cell that can influence presynaptic axon growth or the level of transmitter released by that axon (Fig. 13). Strong evidence in support of the special role for NMDA receptors also comes from work in the three-eyed frog, where infusion of the NMDA antagonist 2-amino-5-phosphonovaleric acid into the optic tectum blocks retinal axon segregation into ocular dominance bands. Subsequently, there have been many other studies that have supported aspects of this model, which has been useful not only in explaining how connections are refined during development but also how plastic changes can occur following different forms of visual experience. Among these studies, those showing that neurotrophin release can be influenced directly by activity and that different classes of neurotrophins and neurotrophin receptors can differentially affect the growth of axons and dendrites depending on the cell

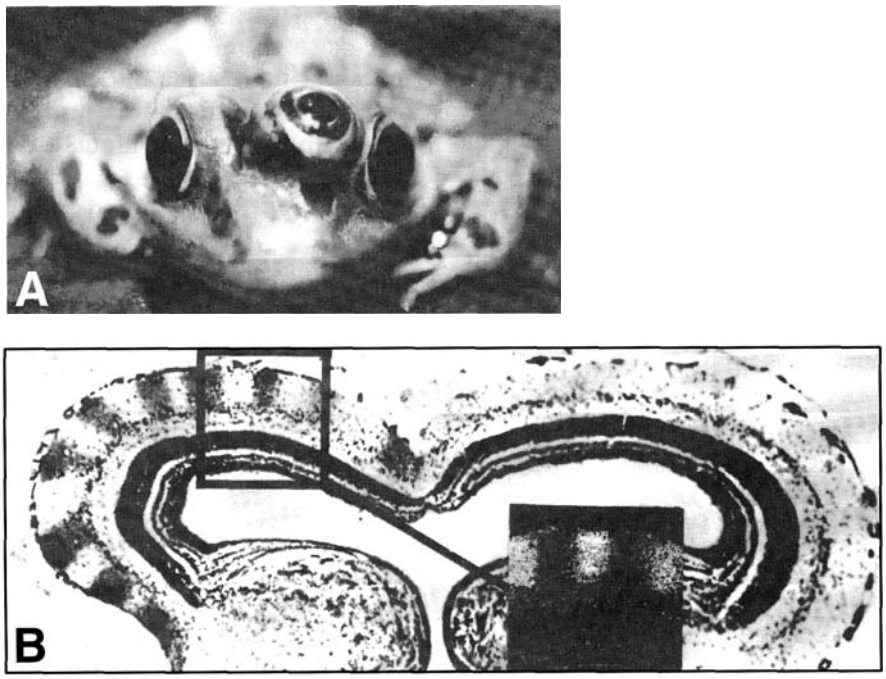

Figure 12 The three-eyed frog. **(A)** Three-eyed frogs have been studied by Martha Constantine-Paton and colleagues. (B) An autoradiograph of the optic tectum showing the formation of stripes of inputs (black and white) from the normal and implanted eye. The inset shows an enlargement under dark-field illumination [adapted with permission from Constantine-Paton, M., and Law, M.I. (1978). Eye-specific termination bands in tecta of three-eyed frogs *Science* **202,** 639–641. Copyright © 1998 American Association for the Advancement of Science].

type are especially relevant because they link activity with other basic cellular mechanisms involved in cell survival and selective outgrowth and targeting of neural processes. In addition to neurotrophic factors and activity-dependent mechanisms, a variety of other factors can impact the development of visual system connections, including, but not limited to, levels of various hormones, a variety of neurotransmitters, and neuromodulators .

For the examples given previously, it is important to keep in mind that although ocular dominance columns do not require visual experience to form in the first place (at least in primates), there are other aspects of vision that do require appropriate visual experience and are not present before birth even in primates. Stereoscopic depth perception, for example, appears to require adequate coordinated activity from both eyes since it does not exist at birth and becomes disrupted if input from the two eyes is not appropriately correlated. Such a situation can arise in humans or other animals that are born and grow up wall-eyed or cross-eyed. In the latter case, stereoscopic depth perception is lost and binocular connections do not form. Only if the eyes are surgically aligned early in a child's life will he or she develop normal stereoscopic vision. Nevertheless, the same activity-driven mechanisms described previously likely operate to allow appropriate binocular connections to form in visual cortex that, in turn, help us to appreciate our three-dimensional world.

IV. CONCLUSIONS

During neural development, cells proliferate and influence each others' fates through an elaborate interplay of extrinsic and intrinsic signals. Cells become committed to specific fates, such as laminar location in visual cortex, early in development before they begin to migrate. Molecular axon pathways are established through a variety of secreted factors and membrane-bound molecules. Correct axon targeting involves gradients of chemoattractant and chemorepellent molecules. Major waves of cell death take place at this stage that help to sculpt connections. Unlike spontaneous neural activity, activity driven by visual experience is not required for basic aspects of axon targeting, map formation, and segregation of axons into ocular territories within the LGN or visual cortex in precocial species such as primates. In all species,

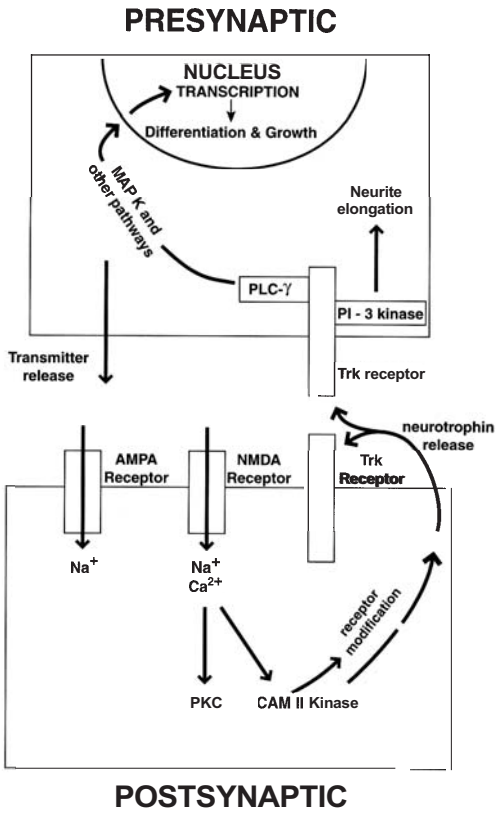

Figure 13 The NMDA receptor channel can open only during depolarization of the postsynaptic neuron from its normal resting level. Depolarization expels Mg^{2+} (not shown) from the NMDA channel, allowing current to flow into the postsynaptic cell. Since the NMDA channel is permeable to Ca^{2+}, there is a significant Ca^{2+} entry into the cell that 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 in an autocrine fashion to influence its own growth via pathways shown in the diagram for the presynaptic terminal/cell. Binding to neurotrophin Trk receptors permits Trk molecules 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 [from Casagrande, V. A., and Wiencken, A. E. (2000). Developmental plasticity in the mammalian visual system. In *The Mutable Brain. Dynamic and Plastic Features.* (J. H. Kaas, Ed.), Copyright © 2000 by Overseas Publishers Association Adapted with permission from Gordon and Breach Publishers].

however, visual system wiring can be profoundly affected by abnormal visual experience, especially during the phase of rapid axonal and dendritic growth.

An elaborate interplay between genetic and epigenetic factors defines specific connections in the highly complex system that is the mammalian nervous system. Molecular cues are important for guiding axons to their general target region and neural activity refines these connections. Even if genetic factors initially define axonal boundaries, it is not necessarily the case that these boundaries are static. The boundaries are partially plastic into adulthood and can be changed even in adults as the result of insult or injury. Neural activity can affect the growth of neural processes and synapses or strengthen existing synapses through Hebbian activity-dependent mechanisms and/or the limited availability of neurotrophins. These same Hebbian mechanisms allow for more limited plasticity in the wiring of the adult brain. Major changes in wiring only occur when processes are growing, but less dramatic changes are possible in the adult and likely involve the same cellular machinery that is used to establish and refine connections normally. The mature visual system at all levels can respond via expression of immediate early genes and regulation of a variety of transmitter and neuropeptide-related molecules to conditions of visual deprivation and damage. Despite the striking similarities that are found between developmental and adult neural plasticity, there are fundamental differences in the developing and adult brain. Younger organisms characteristically seek a variety of forms of visual stimulation and 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 than adult animals that are not. Understanding the neural mechanisms that drive early visual self-stimulation and how these factors interact with the activity-dependent mechanisms discussed to allow for compensation after visual system damage is one of the challenges for future investigations.

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