Chapter 1

The Developmental Neurobiology of Early Vision

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ABSTRACT

The early structural and functional development of the eye, retina, and visual system is best understood in a broad phylogenetic context to see the generality of the developmental mechanisms that specify the developing visual system. The sequence of generation of cell classes in the retina, the control of eye size and conformation, the pathfinding of the optic nerve, and the generation of retinotopic maps all demonstrate the complex interplay of experience-dependent and -independent effects. The generation of the visual cortex, including both primary visual cortex and extrastriate areas, from deployment of the first neurons, specification of cortical areas, and the organization of features like ocular dominance columns and single neuron response properties is a further example of this interplay. New analysis shows that the human visual system is surprisingly mature at birth, ready to assimilate experience. Overall, visual system development employs multiple and apparently redundant mechanisms in production of every adult feature that in concert produce robust and reliable functional outcomes.

The developing human visual system is a spatially distributed assemblage of optical and neural components. These components come informed by evolution as to which must be preformed, which may make use of environmental predictability to inform their own construction, or which might utilize a variable, learning-based organizational strategy. We will briefly review the mechanics of the early generation and specification of the visual system, from eyes to isocortex. The eye particularly is a unique case of a

physical structure directly molded by its own activity. We will contrast generalities with specializations of the visual system by comparing the visual system to the structure of other developing neural systems and by comparing the structure of the human or primate visual system to that of other vertebrates. We will review the contribution of genetic specification, activity-dependent self-organization, and environmental activity–dependent organization to various features of visual system organization including retinotopic map formation, binocular organization, and receptive field structure. Using new information about the relative timing of neural events across species, we predict when visual events occur in the developing human brain and point out some surprising features of the human nervous system at birth.

Overall, we will argue that the process of visual system development is a highly constrained and redundant one, with every well-studied feature showing multiple overlaid production mechanisms that together produce robust and reliable functional outcomes. This redundancy may be understood in the context of "evolvability": Our eyes and brains carry the informational legacy of millions of years of our diverse ancestors' evolution, including those that developed rapidly or slowly, informed by environmental structure or required to develop independently of experience, and those that took their form in daylight or in darkness.

BASIC VISUAL SYSTEM STRUCTURE: EVOLUTION, GENOMICS, AND MECHANICS OF INITIAL DEPLOYMENT

Conservation of Segmentation Genes

Eyes are ancient. Not long ago, the very surprising report was made that the Pax-6 gene, which controls development of the vertebrate eye in the mouse, if transplanted to the genome of a developing fruit fly, *Drosophila*, would cause the production of a *Drosophila*-appropriate compound eye in whatever embryo segment received the transplant (Quiring et al., 1994). Pax-6 is one of a limited and distinct set of genes conserved across vertebrates and invertebrates that are involved in the differentiation of the early embryo into head, body, and appendages, each with their appropriate specializations (reviewed in Callaerts, Halder, & Gehring, 1997). These genes are expressed in an overlapping and nested fashion. They do not control the direct expression of the proteins relevant to visual system function, such as opsin (the protein component of the light-absorbing molecular complex in the retina) or crystalline lens proteins, but rather control the order and coordination of their expression. Subsequently, Pax-6 was found to be important in the coordinated expression of photoreceptor-cell complexes ubiquitously, including those in jellyfish and mollusks, raising the previously unsuspected possibility that eyes are "monophyletic"—meaning the

essential photoreceptor mechanism arose just once in evolution and was elaborated into all its diverse present forms (Callaerts, Halder, & Gehring, 1997). Current debate centers on just what assemblage the Pax-6 gene controls, a multiple-cell complex (Callaerts, Halder, & Gehring, 1997) or just those cells producing opsin (Fernald, 2000).

Phototransduction, the process in which photopigments composed of a retinal-opsin complex react directly to light, is also highly conserved across invertebrates and vertebrates. This is a generality of particular interest for those primarily concerned with human vision—for example, the fact that the opsin complex has a limited number of functional isoforms in all species constrains the kinds of trichromatic color vision that primates may have (Nathans, 1999). In addition, the Pax-6 gene is involved in the development of the olfactory bulb, a structure with which the eye shares many features of molecular biology and embryonic structure. These few examples of many conserved features of molecular biology should serve as cautions to take a very long and evolutionary view when considering anything that might appear to be a specialized feature in mammalian or human eyes—it's probably been done before.

Development of the Eye

The eye primordium everts from the lateral part of the diencephalon (the portion of the forebrain that also includes the thalamus and hypothalamus) and interacts with tissue in the head end that will become the lens (Figure 1.1). As in all parts of the nervous system, neurons are generated in a "ventricular zone" directly adjacent to the ventricle of the primordial neural tube, then migrate toward the outer limiting membrane, most typically in the immediate radial direction. In mammalian retinas, the order of generation is quite stable and may be thought of (with some oversimplification) as occurring in two spatially overlaid bouts (Cepko et al., 1996; LaVail, Rapaport, & Rakic, 1991; Polley, Zimmerman, & Fortney, 1989). The first bout produces components of the diurnal eye, whereas the second produces the nocturnal eye; their combination produces the mature duplex retina. This sequence is depicted in Figure 1.2, using a timetable based on predicted dates for human neurogenesis. The statistical modeling technique that produced these dates will be described in a later section. Retinal ganglion cells that transmit visual information to the brain; cones, the photoreceptors of daylight vision; cone bipolar cells, which connect the cones to the retinal ganglion cells; and horizontal and amacrine cells, which support lateral information transfer within the retina—these begin production first. They are followed by rod bipolar cells, which connect the low-light photoreceptors, the rods to retinal output, additional amacrine cells, Muller cells (the supporting cells of the retina), and finally the rods themselves.

Although the center of the retina is often considered to be the "most

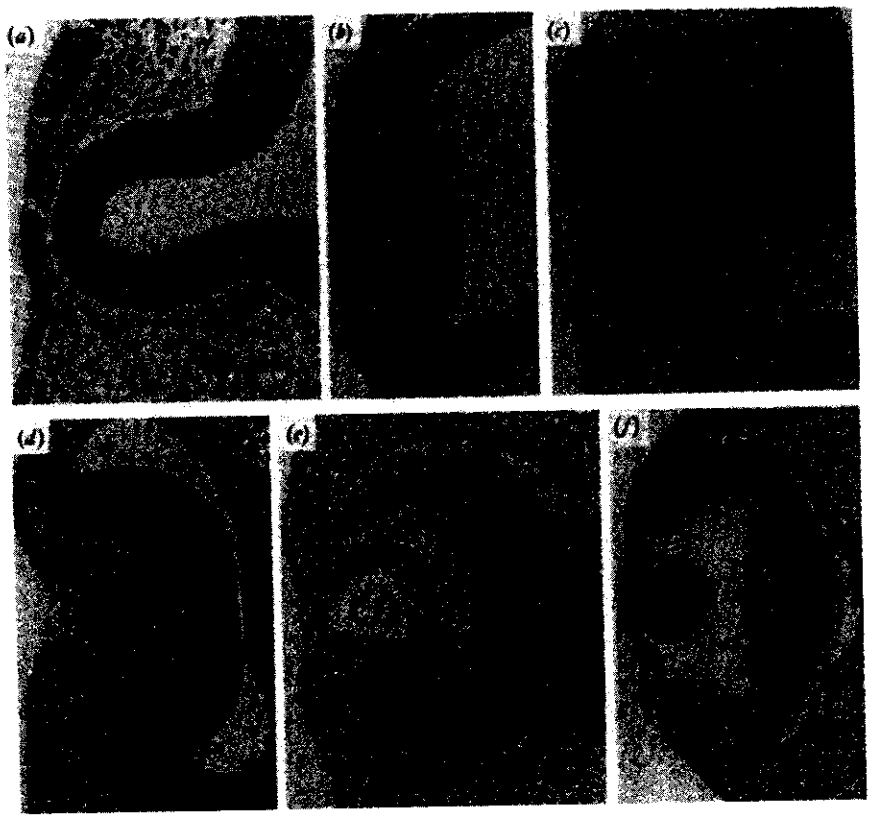

Figure 1.1. Embryonic development of the retina. Photomicrographs of coronal sections passing through the developing eyecup of human (**b–e**) and quokka (a rabbit-sized marsupial) (**a, f**) embryos. Dorsal is toward the top of the page. (a) The optic vesicle of a 16 postconceptional day (PCD) embryo, showing the neuroectoderm contacting the surface ectoderm. (b) Section through a 32-somite human embryo showing the intimate relation between the lens ectoderm and optic vesicle. Note that both tissues are beginning to thicken along the zone of contact. (c) The optic vesicle in a 28 PCD human embryo is just beginning to invaginate to form the optic cup. (d) Section through a human embryo at about 31 PCD showing the optic cup and lens cup in the process of invaginating. (e) A human retina at about 34 PCD. The lens has now detached from the surface ectoderm but still contacts the central part of the retina. (f) Section through a quokka retina aged 22 PCD. The central region of the retina is thicker and is developmentally advanced compared with other parts of the retina. The developmentally advanced region is characterized by the appearance of the first ganglion cells (between the arrows). Reprinted with permission from Robinson, S.R. (1991). Development of the mammalian retina. In B. Dreher & S.R. Robinson (Eds.), *Neuroanatomy of the visual pathways and their development* (vol. 3, pp. 69–128). London: Macmillan.

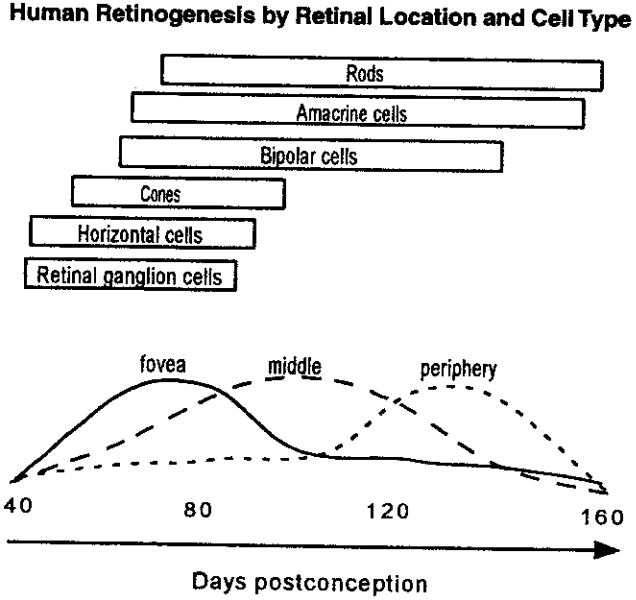

Figure 1.2. Human retinogenesis. The order of genesis of retinal cells occurs in two spatially overlaid bouts. The first produces the components of the diurnal eye, while the second burst produces the nocturnal eye. The dates, which are listed as human postconception (PC) dates, are based on macaque retinogenesis reported by Rakic and colleagues (Angevine & Sidman, 1961) and "translated" into human time from a general comparative database (Clancy, Darlington, & Finlay, 2000, 2001; Darlington, Dunlop, & Finlay, 1999; Finlay & Darlingon, 1995). The curves indicate the timing of production of cells over the entire retinal area (*RGC* = retinal ganglion cells).

mature," it attains this status in a nonintuitive way (Rapaport & Stone, 1982). Neurogenesis begins with the generation of the first ganglion cells and cones over the entire retina, not just the center (Sengelaub, Dolan, & Finlay, 1986). But, as illustrated by the curves in Figure 1.2, cell generation in the primate central retina (not the "fovea," which has not yet formed) barely makes it to the production of the very first nocturnal components (the rod bipolars and rods) before production ceases there, and so a very high central ganglion cell and cone density is stabilized (LaVail, Rapaport, & Rakic, 1991). Photoreceptors and other retinal neurons are continually added in a gradient increasing toward the peripheral retina, thus diluting the relative density of cones and ganglion cells in the periphery and also increasing the convergence of the photoreceptors (cones and rods both) onto ganglion cells. In all retinal areas, the differentiated cells rapidly de-

velop interconnections and also send axons back toward the diencephalon (Maslim, Webster, & Stone, 1986). Some of the elaboration, lamination, and specification of connections between the cells of the retina depends on the normal electrophysiological activity of retinal cells, while some does not (Bodnarenko, Jeyarasasingam, & Chalupa, 1995; Gunhan-Agar, Kahn, & Chalupa, 2000; Wong, Hermann, & Shatz, 1991). This aspect of retinal development has as yet been little studied.

The retina begins its development as an inhomogeneous incomplete sphere, a balloon with areas of greater or lesser thickness, and these physical attributes determine the way the eye will grow in the embryo, fetus, and early childhood (Kelling et al., 1989; Reichenbach, Eberhardt et al., 1991; Reichenbach, Schnitzer et al., 1993). As noted above, the central retina contains a high-density region of cells undisturbed by the continual interposition of new elements—it is both thicker and more mature than the periphery, with more internally connective elements. The peripheral retina is thinner, more elastic, and less mature; in addition, there is a very substantial programmed "apoptotic" loss of cells from the peripheral retina ("apoptosis" refers to an orchestrated program of cell death, not a disorganized dissolution of the cell; Finlay, 1992; Provis & Penfold 1988). As the production of photoreceptors and neurons is concluding, the eye and retina begin to grow and stretch just like a balloon, requiring intraocular pressure for "inflation" (Coulombre & Coulombre, 1956). Because of its inhomogeneous initial condition, the retina undergoes a pronounced differential stretch, with the peripheral retina stretching the most; this will continue in humans into the first year after birth. Note that this fact *absolutely requires* plasticity in intramodal topographic mapping in the central nervous system, as the visual angle corresponding to a particular set of retinal cells will undergo substantial change from birth to the first birthday (Aslin, 1993).

Superimposed upon this mammalian general plan of growth, in primates we find construction of a specialized feature for high-acuity vision, the fovea, studied in detail by Hendrickson and her collaborators (Curcio & Hendrickson, 1992; Hendrickson, 1994). The word *fovea* refers to the half-millimeter pit created by the displacement of the cell bodies of photoreceptors and all other neurons away from the photoreceptive elements of the cones. During development, the outer segments of the cones are reduced in diameter, resulting in a greater absolute and angular density of photoreceptors as the cell processes are pulled to the side. In humans, this process is under way at birth (Curcio & Hendrickson, 1992; Hendrickson, 1994; Hendrickson & Drucker, 1992; Provis et al., 1985a, 1985b) and continues until about the first birthday, thus requiring ongoing topographic reorganization of the retina. Interestingly, the absolute size of the foveal specialization is conserved from the very smallest to largest primates, even though the size of the eye itself may vary greatly. This suggests that the fovea, with its extended fiber processes and unusually limited vascularization, might be at some physiological limit, an idea that receives some support from the high incidence of macular (essentially foveal) degeneration in aging humans (Franco et al., 2001).

Thus, in human infants, we find an eye whose neurons and photoreceptors have been generated and establishing connectivity for at least 6 months prior to birth but whose topological conformation is very much in flux during the first year or so, both in the center of gaze and in the retinal periphery. The quality of the image an infant sees also undergoes substantial change during the first year after birth (see Daw, this volume).

Growing the Eye into Focus

"Emmetropization," the process of matching the length of the eye to the optical power of the lens and cornea, has been the object of much study, both the phenomenon and the mechanisms behind it (reviewed in Troilo, 1992). At birth, human eyes show substantial astigmatism and more variability in focusing an image on the retina than they will after they have had some visual experience (Howland, 1983; Howland & Sayles, 1985). Experience itself is necessary for the improvement. Major changes in eye size, optics, and accommodative ability will occur in the first year or so after birth and continue into early childhood. Prenatal genetic programs, loosely defined as the interaction of the genome and tissues without any corrective effects of experience, delivers a roughly functioning eye to the world, capable of such things as resolving faces, but thereafter experience will direct the details.

How can a developing eye tell that the optical power of the lens and cornea match the length of the eye? The answer lies in the activity of the neural elements in the retina. High-contrast (focused) images produce maximum activity in photoreceptors and their associated neural elements. If the eye has such activity, the optics and length of the eye are matched, and a signal is given to limit growth (Wallman, 1992). However, if the neural elements of the eye are relatively inactive, this creates the problem of determining the nature and direction of the defocus, and the answer to this problem is complex. If the eye is attached to the brain, the brain can produce an accommodative signal to the intraocular musculature to bring an image into focus and thus induce high retinal activity. Evidence exists that the nature of the accommodative signal itself might produce a growth-inhibiting or -enhancing signal (Schaeffel & Howland, 1991).

Independent of a connection to the brain, however, the eye can change its growth rate in response to its activity, though sometimes maladaptively (Troilo, Gottlieb, & Wallman, 1987). If the eye is prevented from forming a focused image at all, it will fail to check its growth, and the condition "deprivation myopia" will ensue, basically forming an eye too long for its

optics (Miles & Wallman, 1990). The effect is local—if just part of the retinal image is defocused, only that part of the eye will show enhanced growth or greater elasticity. Although the full mechanism is not yet understood, evidence points to direct local effects of the retina on cytogenesis or on scleral elasticity (stretching of the tough part of the outer eyeball). There are other potential complications—eye conformation could be thought of as a contest between the requirements of night and day vision, each with different growth requirements. Minimally, it is crucial that low light levels at night not be taken as evidence that the diurnal eye is out of focus, and so the process of emmetropization is also gated by circadian rhythms (Erskine et al., 2000).

Crossing the Chiasm

After the optic nerves, composed of retinal ganglion cell axons, make their way across the diencephalic surface of the eye to the diencephalon proper, there is the problem of getting the information from the two eyes to the proper side of the brain, and from there, into spatial register with one another. To solve this problem, a molecular solution is employed that is similar to the one used to produce commissures in fruitflies and zebra fish. Basically, axons in each optic nerve are attracted to the midline of the diencephalon through interactions with attractant molecules (e.g., netrin, reviewed in Cook, Tannahill, & Keynes, 1998). Once attracted, however, the optic nerves must be induced to leave. The attractant molecule then induces expression of new receptor proteins for the cellular recognition mechanisms, and the initial attraction is turned into repulsion. In most mammals, the situation is complicated in that some axons will leave the midline after crossing to the contralateral side, while others will remain on the ipsilateral side before moving away. Similar to the attraction/repulsion interactions at the midline, the process of selective crossing is also accomplished by specific molecular recognition molecules. Even with such mechanisms, errors of crossing do occur, although typically at a low rate. The aberrantly projecting retinal ganglion cells are later removed by activity-dependent cell death (Sengelaub & Finlay, 1981).

Distribution to Targets

In all vertebrates (e.g., fish, frogs, and mammals) the eye distributes itself to a collection of targets of various functions. These include a hypothalamic structure involved in the maintenance of circadian rhythms (the suprachiasmatic nucleus in mammals); at least two diencephalic structures that transmit visual information forward to the telencephalon (in mammals, these are the visual thalamic nuclei termed the lateral geniculate nucleus [LGN] and the nucleus lateralis posterior or pulvinar, the latter of which also

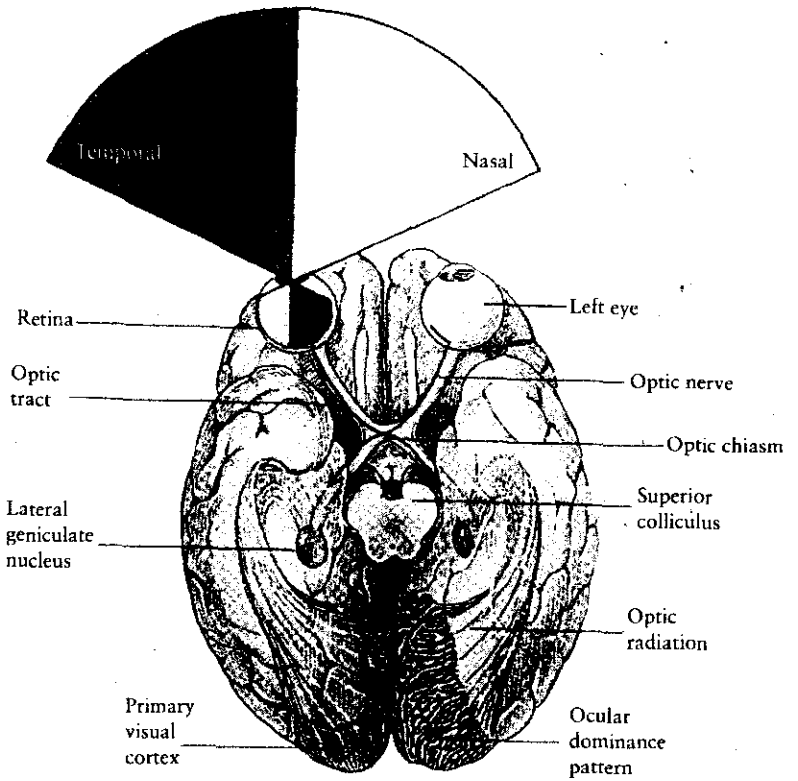

Figure 1.3. General diagram of the visual system. A view of the components of the visual system as viewed from beneath the brain, which has been partially cut away to reveal the internal components. Images detected by the rods or cones in the nasal (inside) halves of each retina reach ganglion cells whose nerve fibers cross over at the optic chiasm to reach their level-two target neurons in the lateral geniculate and the superior colliculus. Reprinted with permission from Bloom, F.E., & Lazerson, A. (1988). *Brain, mind and behavior* (2nd ed.). New York: Freeman.

receives midbrain input), a midbrain structure (the superior colliculus in mammals), and a complex of structures related to the vestibulocerebellum and the oculomotor system (Butler & Hodos, 1996). Most of these targets of retinal input contain topographic (point-to-point) representation of the visual field, often referred to as a visual or retinotopic "map" (Figure 1.3).

We emphasize here the ancient nature of the developmental problems addressed by the visual system. As a result, developmental neurobiologists may select as "model systems" animals distributed widely across the vertebrate spectrum, with good confidence in the ubiquity of the mechanisms they will discover. In the case of retinotopic mapping, the frog, the goldfish,

and the current workhorse of developmental neurobiology, the zebra fish (Easter & Nicola, 1996; Karlstrom, Trowe, & Bonhoeffer, 1997), have been the species of choice.

Retinotopic Mapping

A central and conspicuous feature of brain organization is the topographic representation of sensory surfaces and the preservation of topographic order as one brain structure "maps" to the next. In the visual system, neighboring points in visual space are represented as neighboring points in the thalamus, midbrain, primary visual cortex, and cortical regions beyond. Retinotopic map formation was first investigated systematically by Roger Sperry in the developing optic tectum of the frog beginning in the 1940s (Sperry, 1963). How might such maps be formed? A remarkable number of independent mechanisms can be imagined: (1) The spatial layout of elements in connecting maps could be passively mapped, nearest neighbor to nearest neighbor; (2) temporal gradients could map one element to another in an organized sequence; (3) neighboring elements in a map could actively recognize one another so that the map might travel in a coherent pattern of axons to its target; (4) different parts of the map might have different "road maps" to find different parts of the target; (5) the elements in the first map might recognize locations in the target map at varying degrees of specificity; (6) statistical regularities in the activity pattern of the input array could be used to confer order in the target array; (7) the map might develop from trial and error, based on motor experience in target acquisition.

While a description of each of these mechanisms is beyond the scope of this review, all of these logical possibilities have been shown to contribute to the formation or features of the adult map, sometimes in different species and cases (Fraser & Perkel, 1990; Udin & Fawcett, 1988). Unsurprisingly (given the multiplicity of mechanisms), multiple genes are required for the successful development of a map (Karlstrom et al., 1996). Different features solve the mapping problem at different developmental times; for example, molecular cues are more important early, and activity-dependent organization late. As a whole, this apparent redundancy of mechanisms may be responsible for the robust nature of map formation. That such a host of mechanisms might bear on such an essentially simple problem might be good to keep in mind when developmental scientists in other domains have debates that imply singular mechanisms—"the" mechanism of language acquisition, for example.

At the time of eye opening (in humans, this occurs around the sixth month of gestation, well before birth), the topographic map of the retina is already established in the thalamus and midbrain, and the inputs from the two eyes are already sorted out in the layers of the LGN and the midbrain (Figure 1.3; Rakic, 1976; Shatz & Sretavan, 1986). Studies investigating the intermodal perception of spatial location have demonstrated that a crude multimodal map of space, to be sharpened by experience, is also represented in the midbrain (Knudsen, 1994; Stein, 1984). As with emmetropization, where a roughly useable optics/eye length ratio emerges before the onset of experience, we find an initial mapping of the relationship of auditory, visual, and motor space also appearing prior to experience but one that can be quite substantially altered by experience.

HOW "VISUAL" DOES THE VISUAL CORTEX START OUT? EVO-DEVO EVIDENCE

The Overall Nature of the Cortex

There can be no controversy that the eye is directly adapted to its visual function. But what about the parts of the brain that the retina sends its information to? The most obvious question concerns the primary visual cortex, where both generic and specialized accounts can be offered. For the whole cortex, two kinds of organization have typically been contrasted. At one extreme, the cortex might begin equipotential throughout (O'Leary, 1989), a uniformly connected neural net that will take its adult local specificity from the information and activity relayed via inputs from specific thalamic nuclei and from the negotiations made between the derived cortical areas via their intracortical connectivity. Alternatively, the cortex might begin as a mosaic of specific regions right from the start (Rakic, 1988); that is, cortical areas might begin with specified features particularly suitable for the input they will receive or the functions they will perform. For example, visual cortex might have a complement of neurotransmitters and generate lengths of axonal processes uniquely matched for the temporal and spatial character of visual information, or have a recognition process specific to segregating binocular input (Crowley & Katz, 1999; see also Grossberg, this volume). Inferotemporal cortex might come prewired with the cell assemblies useful for detecting faces in their characteristic orientation and size (see Rodman, this volume). Does the literature on comparative organization of the forebrain, or the early genetic instructions expressed in the developing cortex, suggest that the primary visual cortex or other visual cortices have any special genetic identity that would allow them unique information-processing properties, independent of instruction from visual experience?

COMPARATIVE EVIDENCE THAT VISUAL CORTEX MIGHT BE UNIQUE

From comparative information, primary visual cortex presents the strongest case for unique, area-specific identity of all the cortical areas. As

noted earlier, the primary visual cortex in mammals (also called striate cortex, or area 17) gets its major input from the LGN and contains one visuotopic map. In birds, the area of the telencephalon that receives input from the thalamic homologue of the LGN is called the visual Wulst, which is one part of the "dorsal cortex" (Butler & Hodos, 1996). The Wulst has a layered organization and response properties very similar to mammalian visual cortex (Pettigrew & Konishi, 1976) and appears to be developmentally, connectionally, and functionally homologous to it. Reptiles have a similar organization of the visual system, although nomenclature varies (i.e., the reptilian homologue of primary visual cortex is the dorsal lateral cortex [DLC] rather than the Wulst). The DLC or Wulst is different in structure from the rest of the telencephalon thought to be homologous with isocortex (the six-layered cortex also called the neocortex)—the remaining telencephalon that receives thalamic input consists of nuclear masses without layered organization (Northcutt & Kaas, 1995). Thus, the structural homologue of mammalian visual cortex in birds and reptiles is organized a bit differently than other telencephalic areas. Mammalian visual cortex also has a noticeable peculiarity of organization—although other cortical regions divide into topographically distinct subdivisions as brains enlarge, primary visual cortex does not.

The fact that evolution has selected out and elaborated the visual cortex (in mammals) and its homologues (in other vertebrates) in several different directions suggests that the embryonic precursor of the visual cortex has some feature that makes it easily "visible" to natural selection. For example, a segmentation gene (or genes) unique to the visual cortex but present across species might come to control various other genes involved in the development of particular cortical cell connectivity or neurotransmitter patterns.

DEVELOPMENTAL EVIDENCE THAT VISUAL CORTEX MIGHT HAVE SOME UNIQUE INSTRUCTIONS

Brief Overview of Cortical Development

Similar to the neurons of the retina, the neurons of the cerebral cortex are generated from precursor cells formed in a ventricular zone (Fujita, 1963; Rakic, 1974; Sauer, 1935). Although early cell division in the ventricular zone serves simply to expand the pool of precursor (or progenitor) cells, later divisions of precursors give rise to cortical neurons. The first generation of cortical cells migrates from the ventricular zone into overlying tissue to form the preplate, an early scaffold for later-migrating neurons (Marin-Padilla, 1978). The next generation of cortical cells, which will become layers II to VI, migrates into the preplate and splits it into a superficial layer (layer I) and a deep layer (subplate). Subsequent cortical development

is characterized by an inside-out gradient as younger neurons occupy progressively more superficial positions in the cortex (Angevine & Sidman, 1961).

Similar to migration trajectories in the eye, the majority of cortical neurons travel radially from the ventricular zone (Rakic, 1972), although nonradial migration has also been observed (O'Rourke et al., 1992; Walsh & Cepko, 1988). Embedded within the fundamental laminar structure of the cortex are differences in the tangential plane that emerge during development to give rise to the discrete areas that characterize adult isocortex. For example, in primates, layer IV of the primary visual cortex matures into a thick band of dense stellate cells and myelinated axons. The resulting striped (or striated) appearance of this region, even to the naked eye, is the reason primary visual cortex is also known as "striate" cortex.

Proliferation Rates

Cortical areas may also be distinguished from one another based on differences in the rate of cell proliferation. In primates, the rate of neuronal production in the neuroepithelium underlying primary visual cortex is greater than the rate of production underlying "extrastriate" visual cortical areas, such that the number of neurons in a "unit column" or primary visual area of the adult is twice that of surrounding cortex, principally due to the large number of stellate cells in layer 4 (Dehay et al., 1993).

Transcription Factors

Molecules or proteins known as transcription factors are produced from regulatory genes and serve to activate or repress gene expression by binding to DNA. Transcription factors show unique patterns of expression across the developing cortical plate; most are expressed in gradients (Bulfone et al., 1995; Donoghue & Rakic, 1999; Nakagawa, Johnson, & O'Leary, 1999), and some show striking localization to individual cortical layers (Frantz, Bohner et al., 1994; Frantz, Weimann et al., 1994; Neuman et al., 1993). One developmental regulatory gene, Otx2, is localized to lower layer 4 and/or upper layer V of the visual cortex during development (Nothias, Fishell, & Ruiz i Altaba, 1998).

Although no single expression pattern seems to be confined to a specific cortical modality, the combined expression patterns of various transcription factors do appear to distinguish some cortical boundaries. The combined expression of Lhx2, Emx1, and SCIP distinguishes presumptive visual cortex from presumptive auditory cortex (Nakagawa, Johnson, & O'Leary, 1999), while the combined expression of Id-2 and Tbr-1 marks the boundary between rat somatosensory and motor cortex (Bulfone et al., 1995; Rubenstein et al., 1999). More cortical transcription factors will undoubt-

edly be discovered; it may (or may not) prove noteworthy that several of those currently identified appear to mark the boundaries of visual cortex.

Cellular Communication Molecules

Cell surface–bound receptors and their ligands (molecules that bind to and activate a receptor) also demarcate some cortical boundaries (Donoghue & Rakic, 1999; Gao et al., 1998; Mackarehtschian et al., 1999; Rubenstein et al., 1999). Some of the receptors and ligands specifically identified in cortex are the Eph receptor tyrosine kinases and ephrins, respectively. In primate visual cortex, the early nested expression of the EphA3 and EphA6 receptors delineate primary and secondary visual areas—EphA6 is expressed in both cortices, while EphA3 is expressed only in presumptive extrastriate (secondary visual) cortex (Donoghue & Rakic, 1999). These molecules, similar to those at the visual midline, are believed to serve as guidance cues for developing axons (Flanagan & Vanderhaeghen, 1998). Because the combination of an Eph receptor and its ligand is inhibitory, the expression of one of these molecules in a target may serve to repel axons expressing the other molecule (Cheng et al., 1995; Drescher et al., 1995; Gao et al., 1996). It is likely that the patterns of Eph receptors and ephrins in the visual cortex, as well as in the thalamus, contribute to the establishment of visual-specific thalamocortical projections, as has also been suggested for somatosensory thalamocortical projections (Gao et al., 1998; Mackarehtschian et al., 1999).

INTERACTIONS OF THE VISUAL SYSTEM—EXPERIENCE AND PLASTICITY

The evidence cited above can only give the visual cortex the potential to generate visual perception–specific wiring independent of experience (we use the term *experience* at this point in its widest possible sense to mean any internally or externally generated activity pattern). It should be emphasized that there is little evidence tying genetic instruction of the visual cortex to any particular feature of its wiring. Moreover, it is worth recalling that primary visual cortex retains all of the stereotypical features that make up a typical cortex (layers, connections, and columns). Visual cortex also shows extensive plasticity.

As the visual cortex is generated, it begins to arrange the various overlaid features of adult organization that Hubel and Wiesel (1962) first characterized. These features have been the subject of extensive study and include retinotopy (mapping) (Naegele, Jhaveri, & Schneider, 1988), ocular dominance (a pattern of left-right alternation in thalamic input to layer IV of primary visual cortex [Figure 1.3; Katz & Shatz, 1996; Miller & Stryker, 1990]), binocularity, and orientation selectivity (Wiesel & Hubel, 1974).

The latter feature is "multiscaled"; that is, it includes a range of spatial frequencies. As noted earlier, the LGN initially innervates the cortex in a point-to-point manner (Miller, Chou, & Finlay, 1993; Naegele, Jhaveri, & Schneider, 1988), though there is evidence here, as in most cases, that the map "sharpens" with visual experience.

Activity

Retinal activity, and indeed activity in the entire visual system, begins well before external visual experience. As noted earlier, retinal ganglion cells are the first cells of the retina to be generated, and they extend axons soon after generation—these axons show "spike" activity very early on. Although the inputs from the two eyes will for the most part be noncorrelated, the activity from closely adjoining cells in the retina is more correlated (see Grossberg, this volume). In addition, prior to eye opening, the retina generates systematic waves of activity, "hypercorrelating" the activity of neighboring cells (Wong, 1999; Wong, Meister, & Shatz, 1993). These waves may be a potential source of information for the formation of retinotopy, orientation-sensitive cells, and ocular dominance columns. The details of the timing of many of these events in human development will be discussed more fully later.

Binocular Vision

The case of merging the input from the two eyes has a complex account—the now-familiar multicausal one. Before embarking on a description of development of binocular vision, it would be useful to describe the potential uses of binocularity and how anatomy might reflect them. One use of binocular vision is the redundancy it provides for nocturnal vision (the initiating step for frontal eyes in our primate lineage) whereby two sensory surfaces are used to capture light. In this case, identifying which eye is the source of the information is not necessary. Additionally, binocularity allows the input from the two eyes to be segregated and compared in order to discover contours present in only one eye, sources of object contour information, or depth contours in scenes. In these cases, identifying which eye the signal comes from is of importance. Finally, there is the familiar binocular disparity cue to depth, in which a difference must be computed. Two physical features are tracked when looking at binocular interaction in the visual cortex: (1) the responses of single neurons to visual information derived from either eye and (2) the supraordinate grouping of those neurons into ocular dominance columns. The function of ocular dominance columns distinct from the cell-by-cell convergence of information from the two eyes is not known—intuitively, it would seem useful for those cases where the eye of origin should be tracked for the computation. How-

ever, to our knowledge, there has never been any study linking psychophysical capabilities in binocular vision to the specific properties of ocular dominance columns.

In monkeys and cats, the projections from the two eyes are initially overlaid in the LGN and self-segregate in early development, before birth. A competitive process is implicated, as removal of one eye allows the stabilization of projections to those layers where the remaining eye would not normally project (Rakic, 1981; Shatz, 1990). Endogenous activity of the two eyes (e.g., uncorrelated spontaneous activity or retinal waves) or molecular cues could be the basis of this segregation (Crowley & Katz, 1999, 2000; Wong, 1999). In the developing monkey or cat cortex, the projections from the eye-specific layers of the LGN to layer IV of the visual cortex are already overlaid by the time of birth. The perinatal response properties of individual cortical cells do not differ from those in the adult—there are fully binocular cells, monocular cells, and intermediates, but these cells are not spatially segregated into the ocular dominance column responses seen in the adult. If one eye is made inactive at birth, the other eye retains its spread throughout layer IV and retains physiological influence on the cortical cells. If activity is reduced (e.g., if both eyes are experimentally closed) the segregation into ocular dominance columns is retarded (Hubel & Wiesel, 1965; LeVay, Wiesel, & Hubel, 1980; Stryker & Harris, 1986). If the two eyes are made spatially incongruent and their input is never correlated (i.e., the animal is strabismic), few or no physiologically binocular cells remain (Hubel & Wiesel, 1965). This activity-dependent correlational process is dependent on transmitter/receptor mechanisms in the cortex, and physiological plasticity and transmitter/receptor-mediated plasticity covary (Hensch & Stryker, 1996; Katz & Shatz, 1996).

Recent reports of segregation of LGN projections in the visual cortex of the ferret have been made very early in development, in situations where the role of activity is minimized (Crowley & Katz, 1999, 2000). These studies implicate a molecular mechanism of segregation as well as an activity-dependent one. It is not yet clear if this contradiction with previous studies that have implicated activity-dependence alone might reflect species differences, tracer sensitivity differences, or some other factor. However, if the molecular component turns out to be generally the case, this would make the segregation of ocular dominance columns seem very similar to the other visual functions we have discussed so far (i.e., development of retinotopic maps, control of eye size), in that they depend on both molecular recognition components and activity-dependent mechanisms. No single mechanism "trumps" the others in early development, but rather all contribute to the final conformation.

Orientation Selectivity

On eye opening, cats and monkeys have orientation-selective cells in their cortex, though not so responsive as those found in the adult. However, the complex pinwheel organization of varying orientation selectivity seen in the adult appears very early, before substantial visual experience (Chapman, Stryker, & Bonhoeffer, 1996). It is not really known if the deployment of LGN projections that are slightly more spatially extensive on one axis than another (e.g., giving rise to an oriented cortical cell) is dependent on molecular instructions or on endogeneous activity. Experience with natural images alone is adequate to develop a neural net with the oriented, multiscale properties of visual cortex (Olshausen & Field, 1996); it is not yet known if retinal waves alone are adequate to produce this organization. However, every other piece of information we have about cortex development suggests that a model combining both molecular and activity-driven mechanisms would be a good bet.

In addition to the "classical" receptive field, the axons and dendrites of cortical cells may extend past the immediate cortical column; for example, they may link up extended orientation columns over a wider range of the visual field than that represented by a single orientation column (Fitzpatrick, 2000; Weliky et al., 1995). Initial axon outgrowth is circularly symmetrical and does not show the patchiness and anisotropies of axonal spread that can link oriented contours over several orientation columns (i.e., linking vertically oriented receptive fields along the vertical axis of the entire visual field, and horizontally oriented receptive field along the horizontal axis). Development of these asymmetries is a visual-experience concurrent event and seems highly likely to be directly related to infants' abilities to link object contours and motion over progressively more distant parts of the visual field. It should also be noted that dynamic changes in nonclassic receptive field structure and extent are experience dependent throughout life (Gilbert et al., 1996).

Visual Response Properties in Auditory Cortex

Interesting demonstrations of the ability of a robust developmental process to survive an extreme "dislocation" are the experiments of Sur, Pallas, and others, who were able to induce retinal projections into the medial geniculate (auditory) nucleus of the thalamus of ferrets at birth (Pallas, Roe, & Sur, 1990; Sur, Pallas, & Roe, 1990; von Melchner, Pallas, & Sur, 2000). Removal of auditory input to the medial geniculate coupled with destruction of the lateral geniculate causes a subset of retinal projections to redirect their projections to medial geniculate. The medial geniculate neurons faithfully transmit visual information to formerly auditory cortex, where the cortical neurons are then driven by stimulation of the eyes.

There is a topological feature of the visual system that the auditory system does not share, seen on both a macro- and microlevel of analysis. The macro map of the LGN onto the visual cortex is two dimensional, reflecting the retina (i.e., up/down; nasal/temporal), while the cochlea/medial geniculate typically maps only one dimension (tonotopic) in auditory cortex. At the level of single cells, the microlevel of two-dimensionality in vision is seen in the oriented receptive fields of the visual cortex. Does the experimentally induced medial geniculate representation of visual information in the auditory cortex reflect normal auditory one-dimensionality or visual two-dimensionality? The rerouting studies indicate that at both the macrolevel of retinotopy (Pallas, Roe, & Sur, 1990) and the microlevel of orientation selectivity (Roe et al., 1992) the two-dimensional properties of the retina do appear in the conventionally one-dimensional auditory cortex. It is not known precisely when these dimensional properties are formed, although it is known that alterations in intracortical connectivity are critical (Gao & Pallas, 1999; Pallas, Littman, & Moore, 1999). However, in the ferret rerouting experiments, the manipulation is done pre-eye opening, yet postnatally, so both endogenous and visual experience–related activity might contribute to their expression. Nevertheless, this is strong evidence that activity is adequate to produce some major features of cortical visual map organization, independent of any genetic instructions the visual cortex may have on its own. But note that this *does not* signify that there are no predisposing genetic or molecular instructions in the visual cortex that might normally contribute to the organization of the visual map—almost certainly there are such. The message, as always, is that there are multiple, redundant, cospecifying mechanisms for important organizational features.

Other Visual Cortical Areas

The "Van Essen diagram" (Felleman & Van Essen, 1991), a notoriously complicated-looking map showing all the interconnections of the multiple areas of the visual system, is a map of the adult macaque visual cortex. We know very little about the variability of this map: Do all adult macaques have the same conformation and type of visual areas? Given that primary visual cortex itself can be relatively variable in size from one individual macaque to the next (Van Essen, Newsome, & Maunsell, 1984), the likelihood of variability in the number and type of cortical fields is also very high. We don't know yet if secondary visual cortical areas start out with the retinotopic precision that has been described for primary visual cortex or whether substantial self-organization occurs, as the rewired ferret experiments suggest. We don't know if the partial segregation of the M- and P- pathways that code aspects of temporal and spatial frequency selectivity in adult primates and that show partial segregation in the adult is segregated as well in their early projections. Nor do we know if or when the precise response properties of adult extrastriate cortex, such as the motion selectivity cells of area MT, the face-specific cells of the inferotemporal cortex, or the retinal/ocular position integrating cells of posterior parietal cortex, appear in the relevant cortical areas with or without experience, or at what time. The technical difficulties that these questions pose are extreme, although imaging studies may soon begin to make headway on some of the grosser aspects of these fundamental questions.

HUMAN NEURAL DEVELOPMENT

So far we have been concerned with the multiplicity of mechanisms that produce the various features of developing visual system organization. We have discussed studies that, of necessity, have been accomplished for the most part in the visual systems of nonhuman primates, carnivores, and rodents. However, we do know that in the human infant many of the events discussed above, including eye opening, will occur prenatally (although visual development will extend well into the postnatal period). How can we predict the timing of various neural events in the developing human brain? Virtually no empirical studies are available that can pinpoint such timing. Neurobiologists are severely hampered in this regard because access to human neural tissue is limited and empirical studies that determine when neurons of the retina or cortex are born require invasive techniques. Nevertheless, in this section, we would like to turn attention to timing of events in the human brain, in the particular context of understanding the relationship of structural maturation to behavioral and perceptual maturation.

The Timing of Human Neural Events

We have recently developed a comparative mammalian model (Finlay & Darlington, 1995) that can be used for translating the maturational schedules of other mammals onto human brain development (Clancy, Darlington, & Finlay, 2000, 2001). This modeling approach is possible because (1) the literature on perinatal brain development in mammals has grown so rich in the past decade that our basis for correlation and inference to human development is strong and (2) we have been able to document a striking predictability in the order and duration of neural events across developing mammalian species. Adapting a statistical approach based on general linear models, and using a data set that currently includes 95 different neural events from nine species including mouse, hamster, rat, spiny mouse, rabbit, ferret, cat, monkey, and human, we are able to generate predictions for the timing of developmental events within the human brain, including many aspects of neurogenesis and axonal outgrowth in the visual system (see Table 1.1; also Clancy, Darlington, & Finlay, 2000, 2001).

Table 1.1
Predicted Postconceptional Dates of Developing Human Visual Neural Events

Human Visual Events	Predicted PC Day	(ref.)
Gestational Month 2		
retinal ganglion cell generation begins	38.3	
superficial SC laminae begin	42.0	
dorsal LGN begins	43.1	
RGC axons in optic stalk	46.9	51.0[2]
visual cortex—subplate begins	47.1	
ventral LGN—peak	48.0	
dorsal LGN—peak	50.2	
optic axons at chiasm of optic tract	51.0	
rapid axon generation/optic nerve—begins	52.2	
retinal horizontal cells—peak	52.6	
external capsule appears	52.8	56.0[1]
visual cortex—subplate peak	53.3	
superior colliculus—peak	54.0	
dorsal LGN—ends	54.6	
retinal ganglion cells—peak	55.8	
visual cortex—layer VI begins	56.9	
optic axons reach doral LGN and SC	60.0	
internal capsule appears	60.2	63.0[1]
Month 3		
superficial SC laminae ends	63.0	
cones—peak	66.6	
visual cortex—layer V begins	67.1	
visual cortex—subplate ends	68.5	
visual cortex—layer VI—peak	68.9	
retinal amacrine cells—peak	69.7	
retinal ganglion cell generation ends	72.8	
optic axons invade visual centers	75.2	60.0[1]
visual cortex—layer V peaks	78.0	
visual cortex—layer VI ends	79.1	
visual cortex—layer IV begins	79.9	
optic nerve axon number—peak	81.8	
visual cortex—layer II/III begins	85.8	

Table 1.1 (continued)

Human Visual Events	Predicted PC Day	(ref.)
Month 3 (continued)		
visual cortex—layer V ends	86.4	
visual cortex—layer IV peaks	87.6	
Month 4		
corpus callosum appears	90.9	87.5[1]
LGN axons in subplate	93.1	
cortical axons reach dLGN	95.4	
visual cortex—layer II/III—peak	98.4	
visual cortex—layer IV ends	99.6	
retinal waves begin	107.0–136.0	
superficial SC—start of lamination	106.4	
rods—peak	107.6	
visual cortex—layer II/III ends	108.6	
retinal bipolar cells—peak	116.0	
cortical axons innervate dLGN	116.9	
Month 5		
ipsi/contra segregation in LGN and SC	125.6	175.0[4]
adultlike cortical innervation of dLGN	128.5	
rapid axon loss in optic nerve ends	129.8	
LGN axons in layer IV of visual cortex	130.2	
visual cortical axons in SC	142.6	
Month 6		
eye opening	159.9	182.0[1,2]
Month 9		
synapses surge to 85% of value at puberty		259.0[3]

The timing of various visual neural events, predicted based on comparative mammalian modeling (Clancy, Darlington, & Finlay, 2000; Darlington, Dunlop, & Finlay, 1999; Finlay & Darlington, 1995), is divided into months during human gestation. Note that the second column cites very few empirically derived human events—predictions for the dates of events listed here are made possible only by utilizing comparative modeling.

[1]Ashwell, Waite, & Marotte (1996); [2]Dunlop et al. (1997); [3]Huttenlocher et al. (1982); [4]Robinson & Dreher (1990).

Interestingly, in statistical comparisons with components such as "limbic system," "motor system," and so forth, the visual events across all the species in our data set show the least variability (Clancy, Darlington, & Finlay, 2000). In other words, visual neural events are the most predictable across all species. This suggests that the manner in which the problem of visual function is solved across species is especially conserved, even when comparing rodents, often considered a somewhat nonvisual species, and highly visual mammals such as cats and primates. The absence of statistical variability offers support for the concept that there is something particularly rigid or constrained about the visual system, which forces construction in exactly the same order across mammalian species, even if visual systems as a whole don't end up identical. It also gives us considerable confidence in the predicted dates reported below. Except where noted, these dates (and those in Figures 1.2 and 1.4 and Table 1.1) are based on the "translation" of nonhuman mammalian developmental time into human time using this comparative modeling approach first presented by Finlay and Darlington (1995). The model was subsequently refined as more information became available (Darlington, Dunlop, & Finlay, 1999) and recently adjusted to account for a systematic deviation in timing of neurogenesis in limbic and cortical structures for primates versus other mammals (Clancy, Darlington, & Finlay, 2000).

First Trimester

It is startling to realize how much of the fundamental brain morphology and organization, including almost the entire visual system, is accomplished during the 3 months following conception (Table 1.1). Virtually every neuron in the nervous system is generated in the first trimester, with the exception of the tail of the distribution of the last layer of the isocortex, the external granular layer of the cerebellum, and those few areas in which neurons are generated throughout life. The differentiation of cells into different subtypes and the migration of cells from their birthplace to their ultimate destinations in the retina, cortex, and brainstem occur in the first trimester. The "type" (specification) of a neuron includes many aspects—what shape it has, what information it receives, what transmitters and receptors it produces, and so forth. Some of these features can be specified by location, such that the path taken by a cell as it migrates and its ultimate arrival in a certain brain region will fix some aspects of its "type," while others are set on, or immediately after, generation in the ventricular zone (Cepko, 1999). For example, cells may begin to express various complements of signaling chemicals (neurotransmitters and neuromodulators) before migration, as soon as they are born in the ventricular zone (Lidow & Rakic, 1995).

Second Trimester

This is the period in which the basic patterns of connectivity develop between neural regions. This picture is confirmed in humans by looking for molecular markers that reflect the activity of building axonal and dendritic arbors (Honig, Herrmann, & Shatz, 1996). From a developmental point of view, one of the most important events is the establishment of connections from the thalamus to all regions of the isocortex, including those from the LGN to the visual cortex. These connections are set up during the second trimester in a pattern that resembles the adult pattern from the start, with animal studies showing that visual, somatosensory, auditory, and limbic areas of cortex all receive projections fairly exclusively from those thalamic nuclei that will project to them in adulthood (Miller, Chou, & Finlay, 1993; Molnar et al., 1998; O'Leary et al., 1994). Intracortical pathways (connections from one cortical region to another) also begin to establish their mature connectivity patterns in the second trimester. The corpus callosum makes its first appearance around postconceptional (PC) day 90 and lays down a pattern of homotopic connections (connections between one area of cortex and its corresponding contralateral cortex; reviewed in Innocenti, 1991). The long-range axonal connections start to produce synapses in their target structures in short order, although the bulk of synapse production will occur later (Bourgeois & Rakic, 1993).

Neural development is characterized at many levels and at many points in time by exuberance or overproduction of elements (an additive event), followed by a large-scale elimination of the same elements (a subtractive or regressive event). In addition to the events listed in Table 1.1, most of which are additive, a particular kind of regressive event occurs in the second trimester—apoptosis. This developmental cell death usually occurs in close association with the establishment of major axon pathways between regions and can contribute to removal of errors in axonal connections and numerical matching of connecting populations of cells (Finlay, 1992). Apoptosis can be quite extensive and rapid, often resulting in the loss of the majority of the neurons originally generated. For example, the retina, which establishes connections with subcortical targets in the second month postconception (PC 60), reaches the peak number of axons in the optic nerve less than a month later (PC 82). By the end of the second semester, retinal ganglion cell loss is over, removing as much as 80% of the originally generated cell population (a process that has been directly demonstrated in humans; Provis & Penfold, 1988; Provis et al., 1985a, 1985b). Such cell loss also occurs in isocortex, particularly in the subplate and the upper cortical layers (Shatz, Chun, & Luskin, 1988; Woo, Beale, & Finlay, 1991). Though subplate loss is prenatal, isocortical death in the upper layers may extend into the first couple of postnatal months (O'Kusky & Colonnier, 1982). Overall, this type of early neuronal death seems to serve to grossly

fix cell numbers in interconnecting populations and to fine-tune topographic projections between structures and does not contribute to the fine-tuning of connectional anatomy associated with learning.

The second trimester is also the period in which activity-dependent self-organization of the nervous system begins (PC 107–136), a process best studied in the visual system. In the retina, waves of activity begin to be propagated across the retinal surface, generated by amacrine cells, beginning (in cats and ferrets) after basic connectivity is established and stopping before eye opening (reviewed in Wong, 1999). This organized activity could be a basis for various kinds of categorization in which correlated inputs remain together, while dissimilar (uncorrelated) inputs dissociate, perhaps aiding in establishment of ocular dominance columns prior to extrauterine experience, as suggested by the ferret studies discussed earlier (Crowley & Katz, 1999, 2000). Because retinal waves produce a hypercorrelation of the activity of spatially adjacent cells in the retina, this information might also be used to fine-tune topographically mapped projections or produce more detailed spatial structures like orientation sensitivity in visual cortical neurons. This self-organizing process has some very interesting theoretical implications for developmental psychologists: Activity-dependent organization occupies a middle ground in the nature-nurture debate, where some of the same mechanisms that will be used later for learning from the outside world (i.e., response to correlations in the input) are used in utero to set up the basic functional architecture of the brain.

Third Trimester

By the beginning of the seventh month of gestation, a remarkably large number of human neural events are already complete. The human fetus has matured to the point where the eyes move and remain open for measurable periods of time. Reciprocal connectivity from higher-order cortical areas to primary areas has also begun (Burkhalter, 1993). Pathways exhibit the initial process of myelination (Yakovlev & Lecours, 1967) in which axons are "insulated" by glial cells in order to transmit information more efficiently. Large descending pathways from the cortex continue to develop. Aside from the more obvious role of descending pathways in motor control, the appearance of descending pathways also means that the cortex can already "talk back" to its input regions. In the eighth and ninth months of gestation, a massive and coordinated birth of synaptic connections begins in the isocortex and related structures, which we will discuss in detail in the next section. In general, however, it is fair to say that the human infant is born with a nervous system whose working components are in place and organized. All cells are generated, all major incoming sensory pathways are in place and have already gone through a period of refinement of their total number of cells, connections, and topographic organization. Intracortical and interhemispheric pathways are well developed, though output pathways to such points as the midbrain, pons, and spinal cord lag behind. The primary receptive fields coding such features as motion and orientation selectivity in the visual system are already present, though linkages across receptive fields remain to be elaborated. The primary sensory and motor regions have their adult input and topography, although we do not know yet if all of the multiple subareas described for the primate visual cortex (Felleman & Van Essen, 1991) have sorted themselves out.

SYNAPTOGENESIS

Synapses, the transmitter/receptor complex through which neurons communicate, are central components of neuronal signaling. The production of these synapses (synaptogenesis) and their elimination co-occur over most of early postnatal development, and continue to co-occur throughout life. It is important to note that chemical synapses are only one of a number of ways neurons may communicate—there can be direct coupling between cells (these "electrical synapses" or "gap junctions" are particularly prominent in early development); cells can also communicate through the release of gases, notably nitric oxide (Cudeiro & Rivadulla, 1999; Wu, Williams, & Mcloon, 1994; but see Finney & Shatz, 1998) or by altering the extracellular environment through any means. However, synaptogenesis will greatly intensify during the immediate perinatal period—the surge is recognizable and countable and hence has been much studied.

Although the number of synapses is often used as an index for the amount and complexity of information transfer in a structure, and even though this might be useful in some comparisons (e.g., synapse numbers will increase after certain kinds of experience; Greenough, 1984), it would be misleading to discuss synaptic numbers during development in only this way. "More" in development does not necessarily mean better, more complex, or more mature; it might well mean the opposite. There has long been a controversy about just what the patterns of synaptogenesis are and what they might mean.

Conflicting Views of the Synapse Surge?

Data obtained from the macaque and the human literature have resulted in two hypotheses that are typically presented as conflicting views of synaptogenesis (Bourgeois, Goldman-Rakic, & Rakic, 1994; Granger et al., 1995; Huttenlocher & Dabholkar, 1997; Rakic et al., 1986; Zecevic, Bourgeois, & Rakic, 1989; Zecevic & Rakic, 1991). In one series of studies, Rakic and colleagues described a rapid increase around birth in the number of synapses that seems to take place almost simultaneously across a number of macaque cortical areas, reaching a peak at around the same time in

frontal, cingulate, somatosensory, and visual cortical areas (Bourgeois, Goldman-Rakic, & Rakic, 1994; Granger et al., 1995; Rakic et al., 1986; Zecevic, Bourgeois, & Rakic, 1989; Zecevic & Rakic, 1991). In contrast, Huttenlocher, working with human neural tissue, found that the peak of synaptic density varies between visual, auditory, and somatosensory regions, with the frontal regions not reaching their peak until 3 to 4 years after birth, while the visual and auditory regions peak more closely to birth (Huttenlocher & Dabholkar, 1997).

However, it appears that the story these two investigators tell is actually not very different if the timetables of development in humans and monkeys are appropriately compared. Figure 1.4 depicts replotted data on synapses production in the cortex of the macaque (obtained from tables in Bourgeois, Goldman-Rakic, & Rakic, 1994; Granger et al., 1995; Zecevic & Rakic, 1991) and the cortex of the human (obtained from tables in Huttenlocher & Dabholkar, 1997). To facilitate comparison between the two primates, which have over a 100-day difference in gestation (macaque, 165 days; human, 270 days), the human days were translated into macaque days using our comparative model.

It is clear that what Rakic and Huttenlocher have both shown is that the ratio of synapses to neuropil greatly accelerates just before birth in both the macaque and the human and across a wide variety of cortical areas. In macaques, the peak of synaptic density across cortical areas is reached 2 to 4 months after birth. In humans, the curves are similar to those of macaques, with a marked perinatal increase in synaptic density that begins around birth and flattens postnatally across all cortical areas. It should be noted that synapse counts may, or may not, vary across different cortical regions. However, for methodological and technical reasons, the absolute values of synapse counts should be considered somewhat conditional, especially in human tissue. Moreover, we have attempted to normalize the data by plotting synapse numbers as a percentage of the total at puberty, which we defined as 12 years in human and 3 years in macaque. The "take home" message from the graph lies not in the absolute numbers but rather in the pattern of relative changes. The most interesting feature in both the macaque and the human data lies in the strikingly similar timing of acceleration and deceleration, not in the location of the exact peak.

In order to understand how synaptic numbers are changing, it is useful to place it in the context of brain growth, considering principally "neuropil," the component of cortical tissue including dendrites, axons, and synapses but not cell bodies of neurons or glia nor vasculature (i.e., the synaptic interface). In monkey cortex, the relative proportion of neuropil soars from initially insignificant values around PC 50 to very high values at PC 100, a period corresponding to PC 65 to PC 130 in humans, still well before birth. After that, the amount of neuropil remains constant at about 70% to 75% until about 1 year from birth, after which there is a

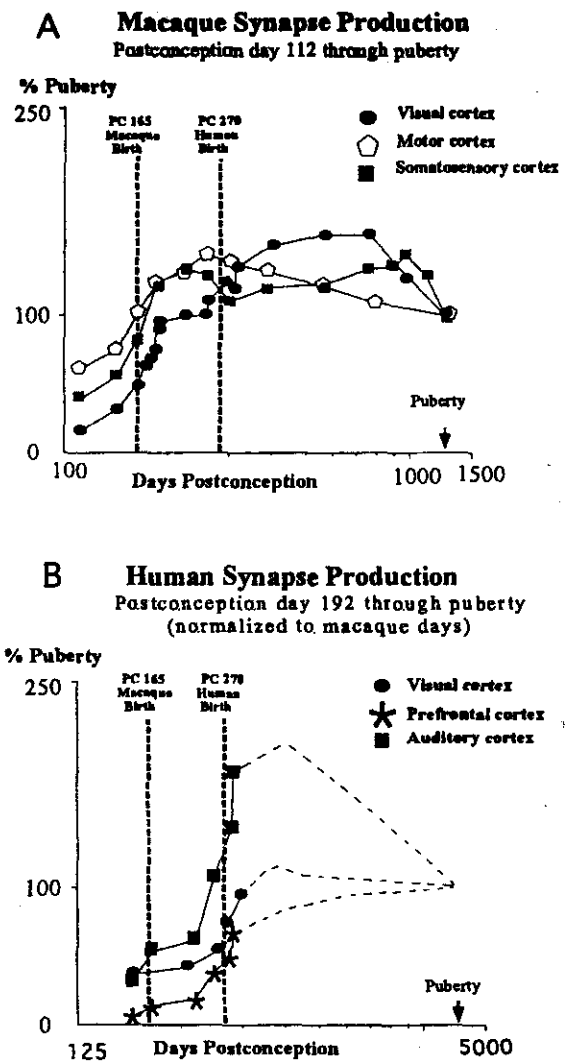

Figure 1.4. Cortical synaptogenesis. A surge in the production of synapses in the developing cortex is coordinated with birth or eye opening (whichever occurs last)—timed to occur just at the verge of an onslaught of experience. The replotted synaptogenesis data from macaque (A) and human (B) cortex depict a rapid increase in the number of synapses coordinated across several cortical areas. If humans underwent an accelerated period of synaptogenesis at the maturational stage of macaques at birth, the synaptogenesis peaking would occur several weeks prior to the opportunity for most environmental stimuli. Synaptogenesis data obtained from Bourgeois, Goldman-Rakic, and Rakic (1994); Granger et al. (1995); Huttenlocher and Dabholkar (1997); Rakic et al. (1986); Zecevic, Bourgeois, and Rakic (1989); and Zecevic and Rakic (1991).

long slow decline to a value of about 50%, reached at some point past puberty. Meanwhile, the whole brain is getting bigger. In macaques and marmosets, the volume of visual cortex (with comparable increases in both depth and surface area) overshoots its adult size by about 45% at 6 months postnatal, then regresses to its adult volume. Overall brain volume increases from birth to adulthood by about a factor of two in monkeys and by a factor of almost four in humans. Because we know that the size of some components like primary visual cortex declines across the same period, the overall increase in brain size must be due to increases in the size of other cortical areas and in the number of glial cells, vasculature, and myelinated fibers in the brain.

What Causes the Synapse Surge?

Using visual cortex as a test case, Rakic and colleagues looked into the possibility that the marked synapse increase is actually *caused* by the barrage of experience that accompanies birth (Bourgeois & Rakic, 1996). However, when monkeys were deprived of visual input, the initial acceleration and peak of synaptogenesis in visual cortex were unchanged, though later events such as proportions, layering, and so forth, did change markedly. But this kind of deprivation experiment might be misleading, because the deprivation itself might induce a host of compensatory changes in other parts of the system. Yet in an experiment in which monkeys were delivered 3 weeks prematurely, so that external experience began much sooner than it would normally occur (Bourgeois, Jastreboff, & Rakic, 1989), there was no effect on the timing of synapse acceleration and peak—it occurred precisely when it should occur, based on the monkey's anticipated gestational birthdate, not the prematurely induced one. Secondary effects on types and distributions of synapses were also seen in this study, so certainly experience does matter. However, experience does not seem to be responsible for the burst in synaptogenesis.

Humans present an evolutionary experiment that is the opposite of the premature delivery manipulation, because we are actually born quite late with respect to many neural milestones (discussed below). Both birth and the accompanying surge of synaptogenesis occur much later in "neural time" in humans than they occur in the rhesus monkey. If humans underwent an accelerated period of synaptogenesis at the maturational stage corresponding to the stage when macaques show rapid synaptogenesis, it would occur several weeks prior to birth (see Figure 1.4). The human fetus would be in possession of a large reservoir of synaptic plasticity to simply contemplate the uterine wall! Timing of peak synaptogenesis to just precede the onset of experience is seen in other primates (Missler et al., 1993) and in animals such as rats (Blue & Parnavelas, 1983) where eye opening occurs after birth (which essentially marks a similar shift from a dark restricted

environment into an onslaught of external experiences). Although less data are available for noncortical regions, a similarly timed burst and decline of synaptogenesis occurs in the striatum (Brand & Rakic, 1984). It should be noted that this peaking of synaptogenesis is the only instance we have found of a neural maturational event tied explicitly to birth rather than to the conserved intrinsic developmental timetable of the brain, which can be quite dissociated from birth (Clancy, Darlington, & Finlay, 2001).

One intriguing possibility for the source of the stimulus for the perinatal synapse surge is raised by work on mammalian parturition from Nathanielscz and colleagues. These recent studies have established that a signal from the fetus to the mother initiates the onset of labor (Nathanielsz, 1998). One could hypothesize that the same signal might trigger the synaptogenesis surge in the fetus itself.

As depicted in the graphs in Figure 1.4, the number of perinatal synapses are well in excess of the eventual adult number. It has become clear, however, that it would be a mistake to view early development as a "regressive" period. In both intermediately aged and mature nervous systems, additive and subtractive events co-occur and overlap (Quartz & Sejnowski, 1997).

MATURATIONAL GRADIENTS

Conventional hierarchical accounts of the development of human perception and behavior appeal to the successive maturation of midbrain versus cortex or the graded maturation of some parts of cortex versus other parts of cortex. Indeed, the hypothesis is often made that a part of the brain might "come online" at a particular point in development. But is there evidence for this?

Intrinsic Cortical Gradients

The isocortex has a gradient of neuron production and maturation that, as noted previously, is well conserved across all mammals. Bayer, Altman, and colleagues have produced detailed studies of the timing of neurogenesis in rodents (Altman & Bayer, 1979a, 1979b, 1988; Bayer et al., 1993), and we are able to apply the comparative mammalian model of Finlay and Darlington (1995) to predict a similar time sequence for humans. Neurogenesis begins at the front edge of the cortex where frontal cortex abuts inferotemporal cortex and proceeds back to primary visual cortex, framing a period of genesis that can last over 30 days in primates from front to back; in humans, this would lead us to expect a neurogenesis window of about 50 days in the first trimester extending from approximately PC 45 to PC 95. The limbic cingulate cortices also get an early start, with genesis beginning in humans about PC 45. The maturational edge possessed by frontal and limbic cortex may be expected to continue in various aspects

of the intrinsic development of those parts of isocortex. For example, more mature neurons may begin to elaborate neuropil and extend local and long-range connections sooner. However, there is little direct association between the time of a neuron's genesis and when it makes its connections, as this also depends heavily on the maturational/trophic status of the regions it will connect to. Paradoxically, the frontal cortex (Fuster, 1997), often described as the last maturing cortical area, is in fact one of the first to be produced and thus quite "mature" in some features.

Imposed Thalamic Gradients

Each region of cortex receives thalamic input by maturity, but the order of thalamic development is different from the intrinsic cortical gradient. In general, the primary sensory nuclei in the thalamus, including the ventrobasal complex (somatosensory), parts of the medial geniculate body (auditory), and the LGN are generated first and establish their axonal connections to the cortex first. Various other nuclei (e.g., those projecting to motor and cingulate cortex) are intermediate in their timing, and the last to be produced are the nuclei that innervate the frontal, parietal, and part of the inferotemporal cortex. It is this thalamic order of neurogenesis that gives rise to the hierarchical notion of cortical development (e.g., "visual matures early; frontal matures late").

However, it is clear that different areas of the brain follow maturational gradients that do not match in order, and many temporal asynchronies are produced. In some areas, intracortical connections will be relatively more mature than thalamic connections (e.g., frontal cortex), and in others, the reverse will hold (e.g., primary visual cortex). This difference in developmental gradients might mean that frontal cortex, the area that bears so much weight in speculation about human evolution (e.g., Deacon, 1997), could be primed for higher-order associative function much earlier than previously thought. A direct comparison of the response properties of frontal versus visual neurons with regard to their responsiveness to thalamocortical and intracortical activation would be an interesting place to begin to explore the functional significance of this anatomical discrepancy.

UNEXPECTED MATURITY OF HUMANS AT BIRTH

There is another conventional developmental notion that should be reconsidered—the idea that neural tissue grows slowly in the human fetus, and consequently the human infant is born in a relatively altrical, or immature, state. This delayed and protracted human maturation is often presented as central to our unusual learning capacity. Clearly much neural development, including in the visual system, occurs postnatally, but is the human infant in fact neurally immature at birth? When we apply the comparative modeling approach to the timing of human neural events, we find instead that human neural development is relatively advanced at birth (Bates et al., 2002; Clancy, Darlington, & Finlay, 2000). This relative maturity makes intuitive sense (certainly to many parents), especially given recent empirical evidence that very young infants are capable of rapid and powerful forms of statistical learning, for example, the probabilistic relationship of syllables in speechlike streams or similar contingencies in visual events (Bates & Elman, 1996; Kirkham, Slemmer, & Johnson, 2001; Saffran, Aslin, & Newport, 1996).

In fact, months prior to parturition, human brains are at the neural maturational state of newborn macaques, primates that are conventionally considered advanced at birth. This human neural sophistication is perhaps best illustrated by fetal eye opening—the human fetus is capable of eye opening almost 3 months prior to birth (note: eye opening, which is difficult to observe in the human fetus, has been empirically determined to occur on PC day 182 of a 270-day gestation [Ashwell, Waite, & Marotte, 1996], although our model indicates it may actually occur about 2 weeks earlier). Why, then, is birth of the human infant delayed relative to brain maturation—and in fact delayed so late that the size of the human infant stretches the birth canal to its very limits?

Allometric analyses of primate data indicate that the human birth weight is above its predicted value, but contrary to conventional notions, the weight is not due to an enlarged brain. The weight is due to a disproportionately large size of the human fetus overall—the brain at birth is actually rather small relative to body size (reviewed in Leutenegger, 1982). It is somatic (nonneural) development that lags into the last months of human gestation (e.g., at 7 months gestation when neural tissue is comparatively developed, human lungs are not yet completely formed, the skin organ is not functioning properly, etc.).

The model translations suggest that despite the somatic immaturity of the human infant the human brain is relatively developed, perhaps even more developed than that of the recognized precocial nonhuman primates. The perinatal surge in synapse production (Figure 1.4), apparently postponed until the onslaught of environmental experience is imminent, may serve to "turn on" a relatively mature human infant brain. These suggestions are supported by recent research that indicates that the human infant rapidly acquires knowledge during the perinatal period, including some learning accomplished in utero (reviewed in Bates et al., 2002). It is even possible that the mismatch between the advanced neural and delayed somatic human maturational schedules is an important component of our learning capabilities, perhaps giving the human infant an enforced relatively nonactive period to observe and assimilate information prior to the extensive motor activity that will accompany later development. The oculomotor system is a relatively advanced volitional action system that can be used at

birth to sample the optic array (Johnson & Johnson, 2001) and can provide a useful perception-action link, but without much physical peril.

SUMMARY

No single strategy holds any monopoly in visual system development. Genetics as well as internal and external activity combine in multiple, redundant, overlaid mechanisms and gradients that all contribute to an overdetermined outcome. Virtually no evidence exists that the visual system, or any other neural area, "turns on" as a unit—most components of the visual system are responsive and plastic, and many change their functional profile as development occurs.

Although there is no evidence for a mosaic organization through which cortical divisions arise via discrete expression of single genes, visual cortex does seem to be a little "different." It has an overtly different structure in nonmammals, it scales differently from the rest of cortex, it is characterized by additional neurogenesis in primates, and it has some regionally specific molecular expression. One question of immediate and central interest is how species-specific recognition mechanisms, such as the recognition of faces and their properties, come to reside predictably in particular cortical areas, such as the inferotemporal cortex in primates (see Rodman, this volume).

The visual system as a whole is a complex and ancient sensory structure and one that has been vigorously studied for its contributions to our knowledge of both development and evolution. It is time to reconsider some conventional notions about such things as neural hierarchies and maturational schedules—just as the first genes that determine the properties of the eyes and brain are expressed in overlapping and nested fashion, so every subsequent aspect of structure and function shows overlapping and piecemeal development. Distinct in our vertebrate lineage, the developing human brain combines a surprising maturity at the time of birth, which could be viewed as readiness for experience, coupled with an unusually long time to assimilate that experience.

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