Visual Development in the Human Fetus, Infant, and Young Child

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The development of the visual system is the most studied of the sensory systems. The advances in technology have made it possible to study the neuroprocesses at the cellular and circuit level. The physical structure of the eye develops early in fetal life, whereas the neurocomponents and connections develop in later fetal and early neonatal life. The development of the visual system involves genetic coding, endogenous brain activity, exogenous visual stimulation after birth at term, and protected sleep cycles, particularly rapid eye movement sleep. Before birth at term, the fetus requires no outside visual stimulation or light. The critical element in development of the visual system before birth at term is protection of rapid eye movement sleep and sleep cycles. Sleep deprivation or disruption in utero and early months of neonatal life causes significant interference with visual development resulting in loss of the topographic relationships between the retina, the lateral geniculate nucleus, and the primary visual cortex in the infant.

The recognition of retinopathy of prematurity (ROP) or retrolental fibroplasia has been the focus of research and changes in clinical care practice for more than 50 years. The early studies in visual development were focused on the diagnosis of ROP and factors associated with cause and frequency of occurrence. The existence of ROP led many investigators to study the development of the human eye and especially the early developmental process that could have an association with ROP.

The processes involved in visual development are the most studied and best understood of all of the sensory systems of the fetus and young infant. The advances in new technology have made it possible to study the processes involved in the building of the visual system at a cellular as well as individual circuit level of detail. The research in early development has been concentrated on four primary parts of the visual system: the retina,[1-4] the organization of the visual cortex,[5,6] the role of endogenous stimulation and exogenous visual experience in the development of the visual system,[7-9] and the role of sleep and sleep cycles.[10-13] So many scientists work with specific aspects of each area that there are more than 10 000 references on aspects of early visual development, the architecture of the visual system, and the function of the visual system.

Components of the Visual System

The primary components of the visual system are shown in Fig 1.[14] They are listed below:

1. Eye
   (a) Cornea
   (b) Lens
   (c) Iris
   (d) Retina
2. Optic nerve and tract
3. Lateral geniculate nucleus
4. Optic radiations
5. Primary visual cortex
6. Superior colliculus (SC)
7. Connections to other parts of the cortex
8. Connections to the limbic system (emotional)
9. Connections to suprachiasmatic nucleus (circadian rhythms)

The basic structure of the eye is under genetic control and has characteristics that are unique to humans. The optics of the eye are made up of the cornea, lens, and iris. The eyelids and the iris function to limit the amount of light entering the eye.
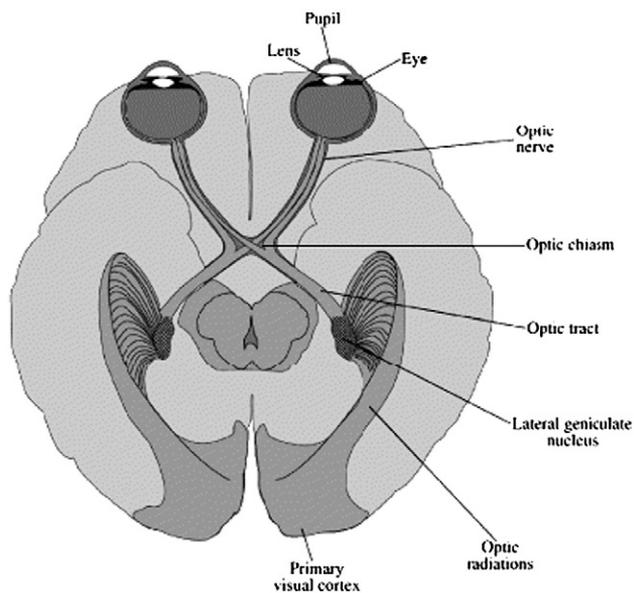
Fig 1. The human brain. The components of the visual system are highlighted and labeled. Reprinted with permission from David Hubel.[14]

The lens is for focus. Preterm infants at less than 32 weeks' gestation have little or no pupillary construction in response to light and have thin eyelids. Thus, they have little ability to limit light exposure to the retina. By term the infant would have consistent pupillary response to light and normal eyelids. The pupillary response to light is usually not consistent until 34 weeks' gestation, and the eyelid is thicker so that by 36 weeks' gestation and beyond, the infant can begin to limit light exposure. At 36 weeks' gestation, the photoreceptor to ganglion cell connections are not yet mature. The key role in the newborn intensive care unit (NICU) is to protect the eye from direct or intense light. Because the uterus is dark, light or visual experience is not needed until birth at term. Preterm birth does not accelerate the timing of the need for visual exposure.

The cellular structure of the retina is shown in Fig 2.[15] In addition to the pupillary construction, the human eye has a dual receptor system in the retina that allows it to adapt to changing light levels during active vision. The retina has two types of receptors for light[16]: rods and cones. The rods are designed to respond to low levels of light. The rods and rod bipolar cells transmit a wide range of light frequencies in low light levels but not color. They are for the scotopic visual system. The cones respond to higher light levels and specific wavelengths. The cones and cone bipolar cells form the photoptic visual system. The retina grows with the growth of the eye. As the eye grows, the rods migrate to the periphery; and the cones migrate to the central areas of the retina. The migration of rods to the periphery and cones centrally in the retina does not require light or visual stimulation. The concentration of cones in the central retina and their connections to bipolar and ganglion cells occur later in development than the bipolar rod connections. The scotopic, rod-based system is the primary system until 2 to 3 months of age. The maturation of the optics of the eye is designed to provide a clear image by term and continues to develop after birth. This allows the infant to accommodate and fixate on visual targets while maintaining clear vision. This is not operative in the preterm infant and matures in the early weeks after term birth.[17]

The staff of NICUs in the 1970s and 1980s, including this author, spent a great deal of energy working with preterm infants trying to encourage attention, focus, and visual tracking. It was believed to be needed for visual development. However, the research on visual development in humans has shown that the preterm infant needs no visual experience until near term and that direct light may be harmful. With preterm infants, the goal of nursing staff, parents, and physicians is to protect the eyes from direct light and provide care in dim light levels, especially when the infant is sleeping.

Knowledge of the structure of the visual system may seem far removed from the care of a preterm infant in the NICU. The timing of the processes involved determines the successful development of the visual system. Much of that development occurs between 24 and 40 weeks' gestation and in the absence of visual stimulation. Thus, environment and care practices in the NICU significantly impact the development of the visual system.

The Retina

The retina is the neurologic part of the eye. All of the neural cells of the retina derive from a single embryonic neuroblastic layer. These cells differentiate into one of five cell groups. Each of these cell groups then differentiate into very specific cell types within the group based on their function and role in the visual process. In addition to the five cell groups, there are three specific layers or eight layers in all. These are shown in Fig 3.[14]

Knowledge of the architecture and processes involved in early retinal development would not be as clinically important if all infants remained in utero until birth at term. Most of the critical processes in retinal development occur between 24 weeks' gestation and 3 to 4 months of age. Unfortunately, many of the processes that occur between 24 and 40 weeks' gestation can be adversely influenced by events in the environment and care of the infant. The environment and care practices usually do not alter the structure (except for ROP) but do affect the function. They impact function more than structure.[18]

Within the eye, there is a pigmented epithelial layer that is directly connected to the pigmented part of the photoreceptors (rods and cones)[10] (Fig 2). There are three basic types of rods and three types of cones. The rods outnumber cones by a ratio of 20:1. Rods connect to bipolar cells through three circuits or pathways that connect to ganglion cells. They are for different light levels. Two types of the rods are low light receptors. They connect to rod bipolar cells that connect directly to a ganglion cell. The third type of rod is for higher light levels. These rods synapse with a cone bipolar cell that connects to ganglion cells via a connection through an amacrine cell (Fig 2). This creates the scotopic visual system that operates in low light. It transmits a full light spectrum but does not transmit color. The scotopic visual system develops during the latter part of fetal life and is operative at term. This is the primary visual system at birth.
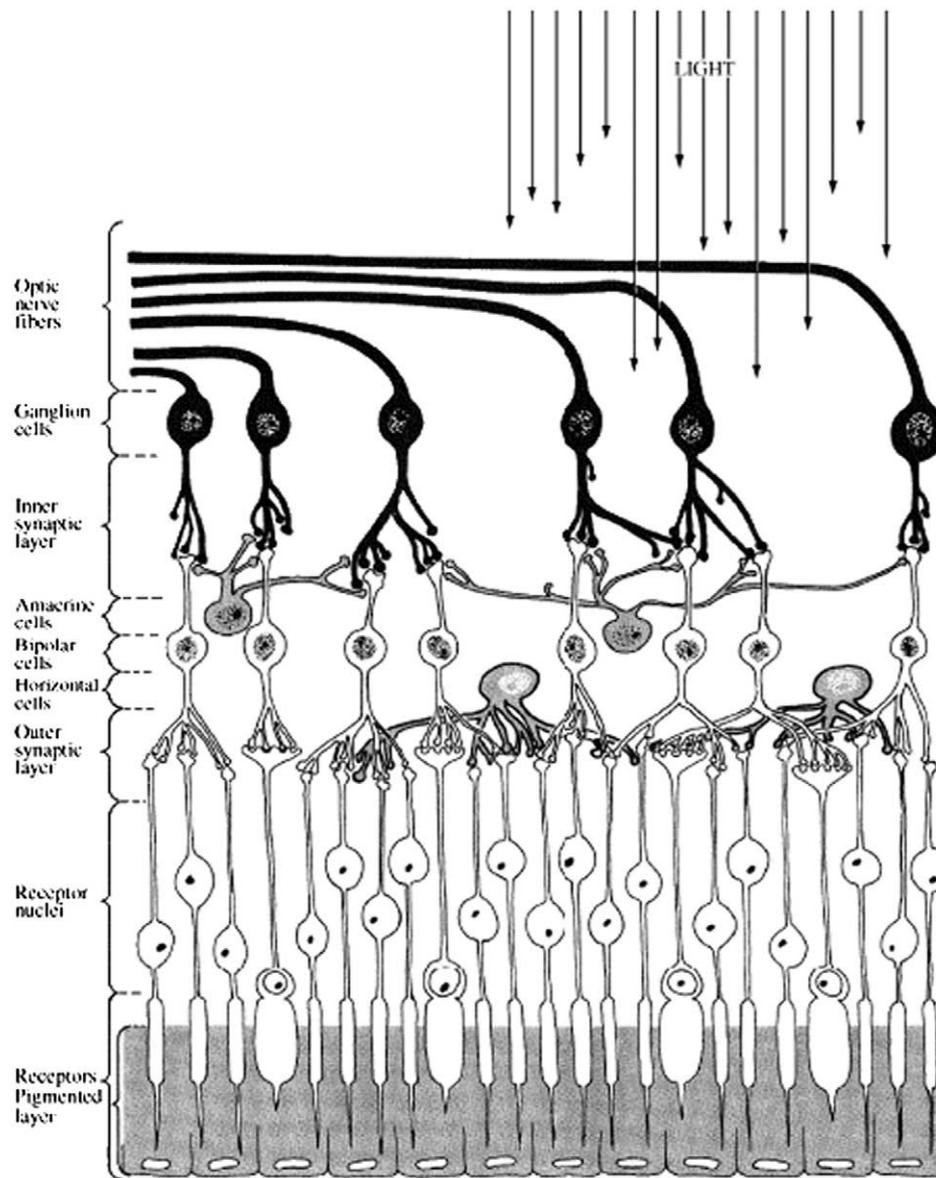
Fig 2. The human retina. The five major cell types and three layers are shown. Not shown are the Muller glial cells which are structural cells and extend across the thickness of the retina from the ganglion layer to the pigmented layer. Reprinted from Palmer, SE., Vision Science: Photons to Phenomenology, pg 30. With permission from © 1999 Massachusetts Institute of Technology, The MIT Press.[15]

Although rods greatly outnumber cones, the connections of rods to ganglion cells often involve multiple rods through a single bipolar cell. Therefore, rods stimulate fewer ganglion cells and have a much simpler neural network. The A1 amacrine cell provides the feedback connection that modulates the signal intensity. This feedback system is not developed until the early months of life and is not available in the preterm infant.

The cones develop connections to several different cone bipolar dells. Some cone bipolar cells connect directly to ganglion cells, whereas other cone bipolar cells connect to ganglion cells through amacrine cells. There are many more cone connections to ganglion cells than rod connections. These form the photoptic visual system. The photoptic vision system using the cone receptors occurs later in development. It becomes operative in the early months after birth at term, but it is not operative in preterm infants. There are significant differences in cone bipolar cells. They differ in molecular structure, numbers, and location of synapses and being *on* or *off* in response to glutamate.

Whereas most mammals have only two types of cones, humans have three types. The human cones are designated red, blue, and green. They are designed to operate in groups across a wide range of light intensities and wavelengths. The cone and the cone bipolar cells also have on and off types. On bipolar cells are polarized by light, whereas off bipolar cells are hyperpolarized by light. The mixture of on and off bipolar cells
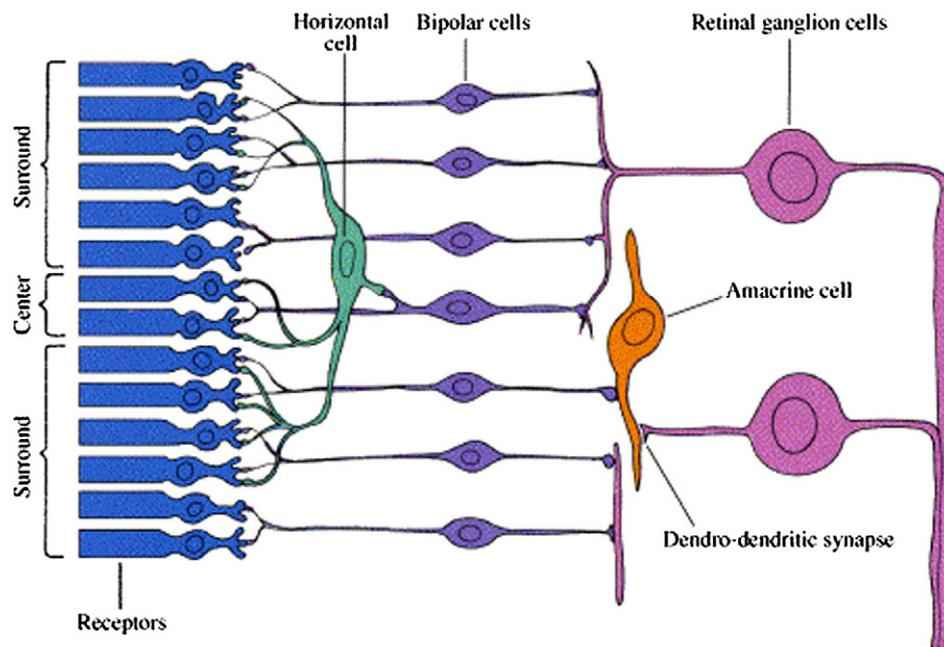
Fig 3. The center surround photoreceptor system. The relationship of the horizontal and amocrine cells to the photoreceptor is essential to the operation of the center-surround system for visual reception. Reprinted with permission from David Hubel.[14]

allows both forward transmission as well as feedback signals that are important in the infant after birth. The cones are divided into short wavelength (blue) and longer wavelength (green and red) types. The blue or short wavelength cone connects with only one short wavelength bipolar cells. For the brain to recognize a specific color, it must receive simultaneous signals from two or more cones. The cones including the bipolar cone connections to amacrine and ganglion cells do not mature to permit color discrimination until nearly 3 months of age. The preterm infant does not discriminate color.[18]

The horizontal cells link different receptors and play an important role in the center surround visual system (Fig 3). They stimulate central receptors and suppress the surrounding receptors. This allows for a clear, sharper central image. The systems of on and off cones, bipolar cells, amacrine cells, and ganglion cells are all needed for the center surround visual system to make a sharp, clear image. There are two types of horizontal cells (C type and L type). They are slow potential cells and remain polarized as long as there is stimulation, even in very low light. They, therefore, retain the image longer.[19]

There are many types of amacrine cells depending on the species and at least 20 types of ganglion cells. The eye, early in development, has a significant excess of ganglion cells. Half or more of all the original ganglion cells created early in fetal life will disappear as redundant by early infancy. The ganglion cells with no amacrine or bipolar cell connection will disappear for lack of stimulation. Each of the different types of ganglion cells transmits different parts of the visual image. The ganglion cells form pathways for transmission that are separate for lines, patterns, depth, movement, color, and intensity. The eye of the young infant has pathways for discriminating differences in light or color intensity before they can discriminate differences in hue or wavelength.[18]

The ganglion cells, when first formed in the retina, will begin a process of random firing. This process is needed to stimulate the growth of an axon toward the lateral geniculate nucleus (LGN) (Fig 4).[14] As the growth proceeds, the firing becomes regular. With the maturation of the starburst amacrine cell, there is the onset of synchronous waves of ganglion cell stimulation that alternate between eyes. These synchronous waves are required for the topographic targeting of the ganglion cell axon in the LGN and the stimulation of the LGN neurons target in the optic cortex. This occurs between 22 and 30 weeks' gestation.[19]

Between 28 and 30 weeks' gestational age, the fetus goes from an undifferentiated brain wave to the beginning of organized sleep states. These are rapid eye movement (REM) sleep and non-REM sleep.[10,11] With the onset of sleep cycles between 28 and 30 weeks' gestation, the synchronous waves of ganglion cell stimulation transitions to pons (P) or pons-geniculate-occipital (PGO) waves originating in the pons and hippocampus θ waves. These spontaneous activated waves occur in the dark during REM sleep. They are essential for the creation of ocular dominance columns in the visual cortex. The PGO waves and the θ waves from the hippocampus only occur during REM sleep. Any environmental event or care practice that interferes with REM sleep or blocks the PGO wave during this period will result in altered development of the visual system.[19]

The axons from the retinal ganglion cells form the optic nerve. These nerves meet in an X pattern in the optic chasm as shown in Fig 1. Half of the axons from each eye go to one LGN. These ganglion cell axons must create a topographic alignment within the LGN and relayed to the optic cortex in an identical
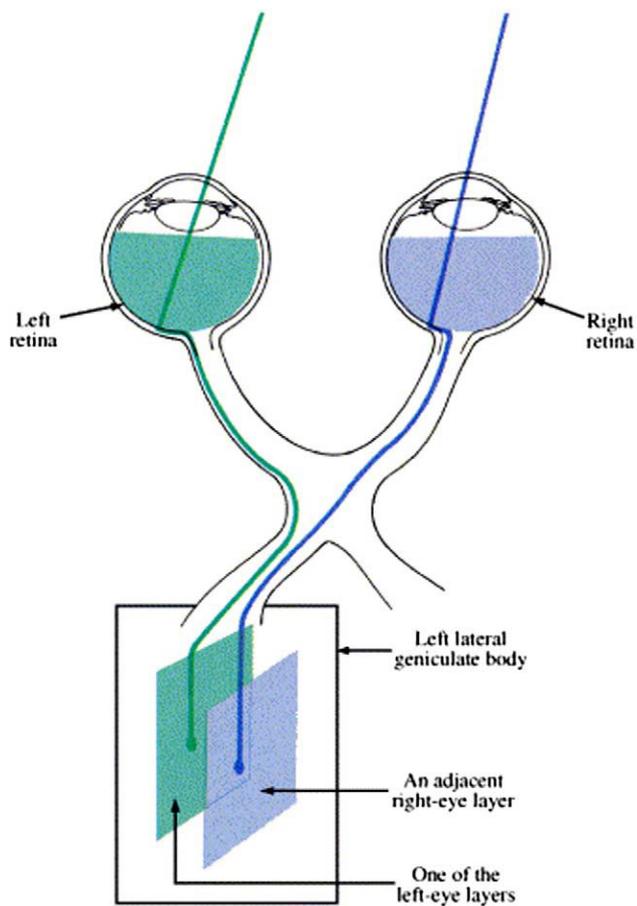
Fig 4. The retinal connection to the lateral geniculate nucleus which receives axons from half of each eye. Reprinted with permission from David Hubel.[14]

topographic alignment. Only with an accurate topographic alignment will the brain receive the image that is identical to the image created in the retina. This develops primarily during the last 16 weeks of fetal life. The connections from the retina to the LGN are shown in Fig 4. The topographic alignment of the LGN is shown in Fig 5.[14] The neurons in the LGN are not aligned in layers and columns until after the onset of synchronized retinal ganglion cell waves. The final alignment requires the generation of the PGO wave from the pons during REM sleep. Disruption of REM sleep in experimental animals results in major disruption in the topographic arrangement of the cells in the LGN as well as failure to develop ocular dominance columns in the visual cortex. This will limit the ability of the infant to develop a full set of visual columns in the visual cortex. The retinal ganglion cell to LGN to visual cortex pathway contains an elaborate feedback system. This feedback system is of less intensity than an incoming signal yet critical to development of the visual system as well as visual function. It modulates the intensity of the signal and is important for the recognition of visual images.[18,19]

Superior Colliculus

The SC is not shown in Fig 1 but is located in the brain stem.[1] It receives axons from the retina and other areas of the brain.[21-23] Its primary function is to regulate and achieve conjugate eye movement needed for depth perception. These connections also require REM sleep to develop. The central area of the SC is where visual, touch, and auditory neurons converge and are integrated into perception of space and spatial orientation. It is necessary to recognize objects and images by three-dimensional shapes. Infants recognize objects by touch
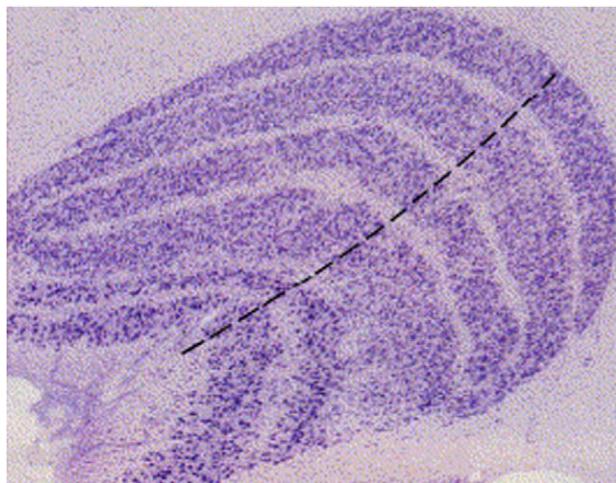

Fig 5. The lateral geniculate nucleus. The lateral geniculate nucleus segregates into six layers that are each related to a single eye. Reprinted with permission from David Hubel.[14]
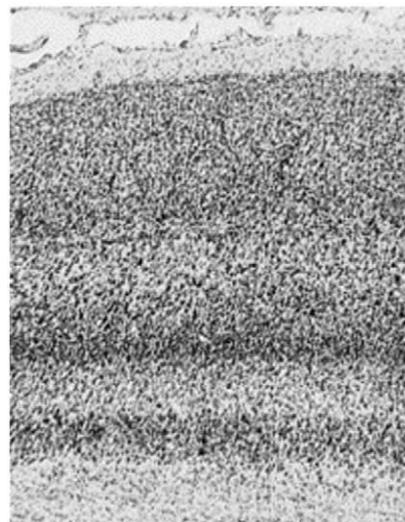

Fig 6. The primary visual cortex. The primary visual cortex is initially organized into six layers of neurons. These neurons must align into vertical columns as a result of activity related stimulation. Reprinted with permission from David Hubel.[14]

(hands and mouth) from birth but visually recognize in three dimensions at around 15 to 18 months of age. This supports the importance of the infant's touch with their own hands and mouth. This begins before term, in utero.

Visual Cortex

The visual cortex is located in the back of the brain in the occipital lobe (Fig 1). The neurons in the visual cortex are formed in the germinal matrix in the center of the brain and migrate to the cortex to form six layers (Fig 6).[14] These cells must be stimulated so that they will move to form columns. The initial columns are called *ocular dominance columns* and begin formation during the last 8 to 10 weeks of gestation. These columns require REM sleep and the stimulation of the PGO waves. These columns form the framework for the development of directional columns. Directional columns are required for seeing lines, patterns, and movement. They require specific visual experience and will fail to develop if the infant is deprived of visual experience in the early months of life. The failure to develop directional columns after birth if deprived of specific visual experience was discovered by Hubel and Wiesel[5,6] and was the basis for their Nobel prize. There must be separate columns for lines and movement in all directions. There must be separate columns for lines and movement in each 5° of arc or 36 for a full circle to see all parts of a visual image or movement.

Cortical Connections

All of the columns in the visual cortex must connect with related areas in the other areas of the brain. Connections include the temporal lobe, parietal lobe, and prefrontal cortex. These areas are essential for long-term brain development, especially the prefrontal cortex. These connections are essential for the brain to convert visual images into perception, recognition, discrimination, importance, and memory retention. These primary connections occur between birth and age of 5 to 6 years.[19,20]

Visual Development—Structure and Function

There are four basic processes that determine or greatly influence the overall development of the visual system. These processes begin very early in fetal life and continue throughout the individual's lifetime. Any of these processes can be altered by toxic exposures and specific exposures that create interference with the sensory development processes.[7-9,19]

Genetic Endowment and Genetic Expression

The processes involved in the basic structure of the brain, peripheral nervous system, and sensory organs are under genetic control and respond to genetic code. These include cell division, cell differentiation, cell migration, organ formation, and initial cell location and alignment. The basic structure and organization will proceed in the absence of activity or specific stimulation. In the development of the eye, the cells of the retina differentiate and locate in the retina by genetic code and in the absence of any visual stimulation. The Müller glial cells are structural cells that provide the genetic signal molecules that direct both the axon and dendritic growth from the retinal ganglion cells. The growth and targeting of the retinal ganglion cell axons are the results of genetic code. The connection from the retina must proceed to create a topographic relationship with the LGN and cortex. These are all independent of visual activity.

Epigenetics are the processes and the factors from the environment that alter the expression of individual genes without altering the basic structure of the DNA. Epigenetic change in gene expression can be the result of nutritional factors or deficiencies, toxic exposures, or sensory exposures. These can alter not only how the gene is expressed in the mother and fetus but can affect the genes in the eggs of the female fetus to alter the gene expression in the next generation. This can affect the genetic expression needed for healthy visual development.

Stimulus or Activity-Dependent Processes

The genetic code places the components of the visual system in their initial location. The next processes require stimulation. These processes come in two forms: endogenous or internal and exogenous or outside visual stimulation. The first and most important, coming early in the development of the visual system, is the endogenous or internal brain-generated stimulation. This occurs in the visual system with no outside visual stimulation. The internal or brain-generated cell activity is required for the development of all of the sensory systems and parts of the cerebral cortex, hippocampus, thalamus, brain stem, spinal cord, and auditory system. The purpose of the endogenous stimulation is to create permanent circuits and critical relationships. It prepares the system for outside stimulation. In the case of visual development, this endogenous stimulation prepares the system for vision and visual stimulation after birth at term. The endogenous stimulation in the visual system starts with the random, spontaneous firing of retinal ganglion cells. This is needed to start the growth of the axon. This ganglion cell stimulation soon becomes regular firing. With the maturation of the starburst amacrine cells (one of the first to mature), the ganglion cell firing becomes synchronous waves that alternate eyes. This starts the process of segregating the cells of the LGN into one of six layers (Fig 5). This occurs at around 22 to 29 weeks' gestation. The electroencephalographic brain wave pattern is one of immature undifferentiated waves. At 29 to 30 weeks' gestation, the brain begins to mature to a differentiated sleep pattern with brief alert periods or cycles of REM sleep and non-NREM quiet sleep or slow wave sleep interspersed with periods of nonsleep activity.[24-27]

When there is partition of the sleep, the synchronous waves from the retinal ganglion cells transition to P or PGO waves from the pons in the brain stem and θ waves from the hippocampus in the temporal lobe. These waves also occur in the dark during REM sleep. These waves are disrupted by anything that interferes with REM sleep or drugs that depress

the function of the pons or cortex. These waves refine the six layers of cells in the LGN and cause the connections between layers to disappear, and they become topographically aligned with the ganglion cells of the retina.

The starburst amacrine cell has two types of connections to the retinal ganglion cell. One is a regular synapse with the ganglion cell dendrites, and the other is a gap junction connection directly with the cell body. The gap junction connections are easily disrupted. Any process or drug that blocks either the retinal ganglion cells or the PGO wave from the pons will result in a disordered organization of both the LGN and the visual cortex. The spontaneous ganglion cell waves, the PGO waves from the thalamus, or the θ waves from the hippocampus are all related to REM sleep. They are essential to the development of the visual system.

Exogenous or Outside Stimulation or Activity

Visual activity or stimulation from outside through the eye is also essential for visual development after birth at term. At this point, the human infant's eyes and visual system are then ready for vision. After birth at 40 weeks' gestation, the infant has pathways from the retina to the visual cortex and can receive stimuli from lines, patterns, movement, and different light intensities, but not color. The color pathway begins to operate at 2 to 3 months of age. The first color the infant discriminates is red.

Visual experience requires focus, attention, novelty, and sufficient contrast to see shape and lines. It must have regular visual experience to maintain the continued development of the visual system. Infants and young children who spend most of their time in deprivation surroundings with little stimulation not only do not develop new visual circuits but will lose existing circuits because of the atrophy of disuse.

The primary period for development of the visual system is the critical period between 20 weeks' gestational age and 2 to 3 years of life. Most of the critical components of the visual system are complete by age 1 year. Visual development is not just a problem of protecting synchronous waves of ganglion cell stimulation and REM sleep in the NICU but is also an issue for infants after 40 weeks in deprivation environments at home or in day care settings. They require both protected sleep time and regular, meaningful visual stimulation when awake.

The synchronous retinal waves as well as the visual connections are cholinergic and are inhibited or disrupted by anticholinergic drugs and nicotine. The gap junction connections are inhibited or disrupted by alcohol. The combination of alcohol and nicotine can disrupt both types of connections between amacrine cells and ganglion cells. Interference with REM sleep cycles also interferes with organization of the LGN and visual cortex as well as other sensory systems.

The period of retinal ganglion cell waves begins before the photoreceptors are developed and the sleep is partitioned. Once sleep cycles begin and sleep is partitioned, the ganglion cell waves shift and become patterned activity in the dark during REM sleep. The retinal ganglion cell waves are altered with the onset of sleep cycles. The exact time of the transition is not known but is around 30 to 32 weeks' gestational age. At this time, they become especially susceptible to disruption or suppression by deep sedation (fentanyl) or other agents that suppress neurons and ganglion cells. They are also disrupted by strong competing stimuli such as pain, intense noise, unusual movement, and bright light. Flickering lights may also interfere with visual development.

After 38 to 40 weeks' gestation, the visual system is activated by light and requires visual experience for continued development. Directional columns for lines, patterns, motion, and, later, color perception require visual experience. This continues through the first 3 years of life, the critical period for visual development.

For healthy visual development in infants after birth at 40 weeks, the visual experience requires (1) light on objects, not direct light; (2) focus; (3) attention; (4) novelty or change; (5) movement; and, after 2 to 3 months, (6) color. The mother's face is of prime importance. Focal distance for an infant is 10 to 12 inches and gradually increases with age and ability to focus. Direct light in the eyes should be avoided in the NICU and at home. The development of the horizontal cells and amacrine cells is needed to support the center surround system for sharp image formation. Absent or abnormal visual exposure (ie, direct bright light) can interfere with the development of the horizontal and amacrine cells and their role in developing the center surround visual system.

Care practices in the NICU should consider the gestational age and sensitivity of the infant as well as the visual array that is offered in the environment. Of prime importance is the avoidance of direct light in the infant's eyes, particularly for the youngest, because their eyelids are translucent, allowing in ambient light, and are open for a significant amount of time.[27] As they are unable to protect their own eyes, it is the responsibility of the caregiver to provide that protection. In emergency situations, when increased lighting is necessary for visualization, extra precaution should be taken to protect the infant's eyes, as the time of stress will compound the effects of light on their physiologic organization.

Stimulation of the visual system at or after birth at term is best facilitated by the infant being provided the species specific visual array of the mother's face. Positioning and lighting such that the infant is "en face" or approximately 8 to 12 inches from the mother's face maximize visual regard. To enhance the infant's ability to look at the mother's face, dim ambient lighting, with some light directed on the mother's face, may allow the infant to locate the contrast of the mother's features such as her hairline, eyebrows, and mouth. Other visual targets are not necessary for the development of the visual system and may cause physiologic disorganization, particularly if not timed according to the infant's state availability.

The contribution of REM sleep to the developing visual system is well documented. Identification of infant sleep states can be done for planning and carrying out care practices according to the availability of the infant and for helping parents to know when the infant needs to be undisturbed. Several sleep classifications systems have been developed for both term[28] and preterm infants[29-31] and can be used to identify the behaviors indicative of REM sleep.

The human visual system will develop well if attention is paid to the environment to protect endogenous stimulation and the avoidance of drugs and intense conflicting sensory exposure. When the visual system is ready for external visual experience, it must involve interaction with a care giver, be in focus, have the infant's attention, and provide meaningful stimuli and visual opportunity.[7,19]

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