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"Development of Visual Centers in the Primate Brain Depends on Binocular Competition Before Birth"

Pasko RAKIC
Yale University
School of Medicine
Section on Neuroanatomy
New Haven, CT
USA

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SCIENCE

Development of Visual Centers in the Primate Brain Depends on Binocular Competition Before Birth

Abstract. *Removal of one eye before birth permanently changes the cellular organization and synaptic connectivity of visual centers in the primate brain. The most notable alterations are (i) the lateral geniculate nucleus develops only two cellular layers and one interlaminar fiber band instead of the normal six layers and five bands, (ii) aberrant synaptic connections are formed between the intact eye and the geniculate neurons that have lost their normal input, and (iii) ocular dominance columns fail to develop in the visual cortex.*

It has been known for some time that monocular enucleation or sensory deprivation in the neonatal period causes functional and structural alterations in the visual system of mammals (*1*) including primates (*2*, *3*). The effect is particularly prominent in the dorsal lateral geniculate nucleus (LGd), which in most Old World primates as well as in humans consists of six horseshoe-shaped cellular layers separated by five fiber-rich interlaminar bands (Fig. 1A). Three of the layers (1, 4, and 6) receive input from the contralateral eye (Fig. 1B) and the remaining three (2, 3, and 5) from the ipsilateral eye (*4*). The LGd neurons subserving each eye project to layer IV of the visual cortex (Fig. 2D) in the form of separate and alternating ocular dominance columns (*5*). The two ventralmost layers of the LGd contain large cells and are termed "magnocellular," while the upper four layers have smaller cells and are called "parvocellular" (Fig. 1A).

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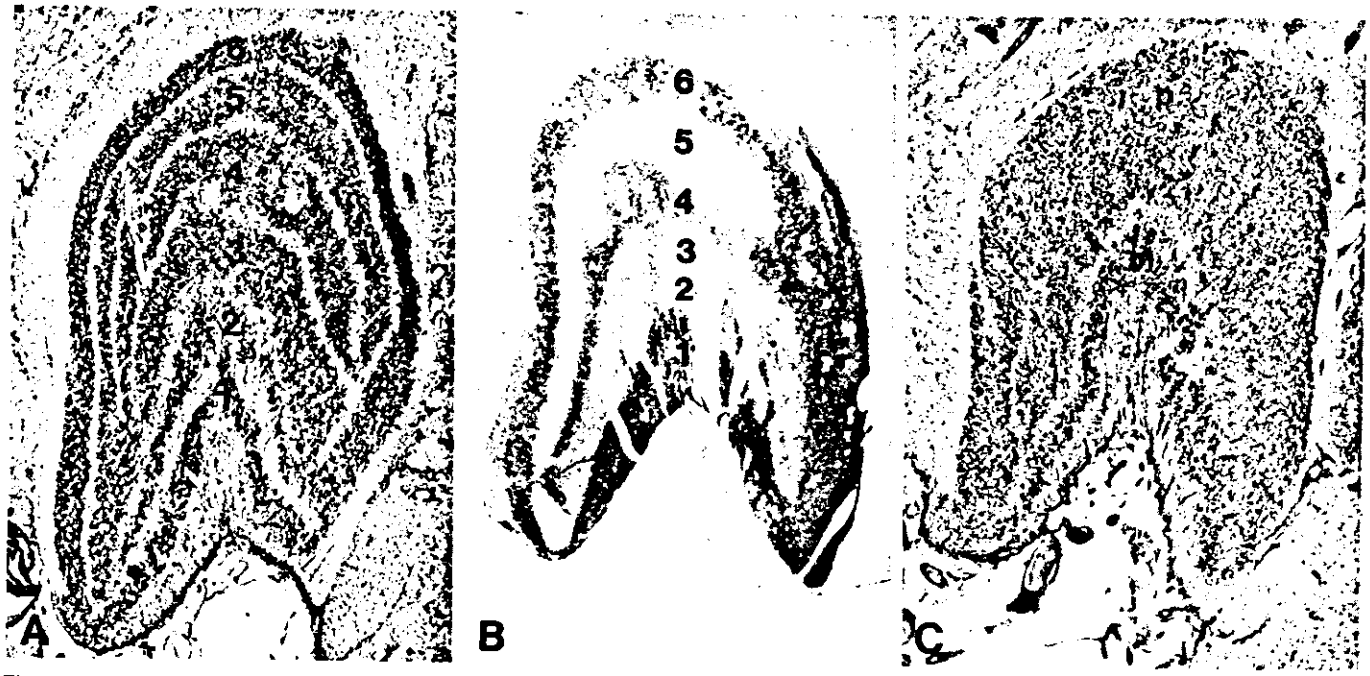

Fig. 1. (A) Nissl-stained coronal section of the lateral geniculate nucleus (LGd) in a normal adult monkey, showing six cellular layers (1 to 6) and five interlaminar bands. (B) Autoradiograph of the LGd of a normal adult monkey showing labeling of layers 1, 4, and 6 after injection of the contralateral eye with radioactive tracer. (C) Nissl-stained LGd in a monkey of the same age from which one eye was removed at the second fetal month showing the presence of the magnocellular (*m*) and parvocellular (*p*) moiety and the absence of the normal six-layered pattern.

The parvocellular and magnocellular moieties of the monkey LGd project to different sublayers of the cortex (*6*) and belong respectively to the X- and Y-like systems, which among their other functional properties are presumably related to color and noncolor vision (*7*). Although these features of LGd organization in primates are not fully understood, the developmental mechanisms and the biological significance of cell segregation into separate layers and functional subsystems have been of considerable practical and theoretical interest (*3, 4, 8*).

This study was initiated after pilot experiments in the monkey indicated that enucleation of one eye before birth had even more profound effects on the structure of the LGd than when performed postnatally (*9*). This can be expected, since in primates all LGd neurons are generated (*10*) and their basic connections established before birth (*11*). It should be emphasized, however, that retinogeniculate projections from the two eyes overlap before sorting out into three alternating layers in the LGd during the second half of gestation (*11*). Furthermore, the geniculocortical terminals are also initially intermixed before becoming segregated into ocular dominance columns (*3, 11*), and the projections from magno- and parvocellular layers of the LGd are unseparated before becoming distributed into appropriate sublayers of layer IV (*11*). Thus, enucleation of one eye before birth can reveal the extent to which competition between axons originating from two eyes may influence the development of binocular or X- and Y-like neuronal systems (or both) in the absence of any visual experience.

Twelve monkeys (*Macaca mulatta*) were studied. Two animals in the second month and two in the third month of pregnancy were subjected to hysterotomy; the fetuses were temporarily removed from the uterus and, after eye enucleation, replaced in the uterus (*11*). Pregnancies were carried to full term (5½ months), when each fetus was delivered by cesarean section and allowed to develop to the ages of 2 months to 1 year. In two of these animals, a mixture of [^{3}H]proline and [^{3}H]fucose (total of 1.0 to 1.5 mCi) was injected into the vitreous body of the intact eye 14 days before they were killed. As a control, four normal fetuses corresponding in age to that at the time of eye enucleation and four postnatal monkeys corresponding in age to that at death were processed in a similar way. In each brain, a 0.5- to 1.0-mm thick coronal slice was dissected from the middle level of the LGd contralateral to the eye injection and processed for electron microscopic analysis. The remainder of each brain was processed for autoradiography (*11*).

In the two monkeys in which one eye was enucleated during the second fetal month, the LGd was located in its usual position and was normal in size and shape (Fig. 1C). Although the cell packing density may have been slightly altered, the number of neurons was not significantly diminished. The most dramatic finding was the absence of six cell layers and all but one of the interlaminar bands in the LGd (Fig. 1C). The single remaining interlaminar band was situated between the magno- and parvocellular moieties and presumably corresponds to the space between layers 2 and 3 that normally receives input from the same eye. In the two monkeys in which one eye was enucleated at the end of the third fetal month, the LGd also attained a normal position and external shape, but the dimensions of the nucleus were smaller than in the animals operated on 1 month earlier (*12*). In addition, these specimens contained some indication of layers comparable to the stage of lamination that existed at the fetal age when the surgery was performed. Thus, the ingrowth of projections from both eyes during the first half of gestation is essential for both the initiation and completion of cellular lamination in the monkey LGd. However, the segregation into magno- and parvocellular moieties of the nucleus proceeds normally in the absence of one eye.

When radioactive tracer was injected in the remaining eye of the adult monkeys that had been enucleated at fetal month 2, anterogradely transported label was distributed over the entire LGd (Fig. 2A). Thus, the neurons in the positions normally occupied by layers 1, 4, and 6, which should receive projections from the removed, contralateral eye, received

ipsilateral input equivalent to that received by neurons situated in positions corresponding to the appropriate layers 2, 3, and 5. Furthermore, electron microscopic examination revealed that typical retinal synapses were present at positions of all presumed layers (Fig. 2, B and C). Therefore, the axons that originated in the remaining eye probably formed synapses with all LGd neurons. The functional significance of this abnormal synaptic arrangement is unknown, but the changes seem to be long-lasting since they were observed in a 1-year-old monkey lacking one eye from the early fetal age.

When one eye was removed at fetal month 3 and the remaining eye injected with radioactive tracers after birth, label was also distributed rather diffusely over the LGd. In this case, however, small, elongated, less densely labeled territories were visible within the posterior pole of the nucleus in a pattern similar to that described in normal 3-month-old fetuses (*11*). Therefore, even after the process of separation of the terminals originating from two eyes has begun, it is arrested if one eye is removed during the formative period.

In the visual cortex, transneuronally transported radioactive label injected into the eye of mature monkeys that were monocularly enucleated at prenatal periods formed continuous horizontal sheets localized mainly within layer IV without any indication of the alternating ocular dominance columns (Fig. 2E) that are characteristic of the normal visual cortex in this species (Fig. 2D) (*3*). The vertical segregation of the parvocellular and magnocellular moieties of the LGd input into sublayers IVA, IVCα, and IVCβ was still achieved, however (Fig. 2E).

These results indicate that the integrity of projections from the two eyes during prenatal development is necessary for the establishment of normal cell distribution and synaptic organization in the primate visual system. More specifically, competition between the two eyes is essential since neurons and their interconnections formed abnormally even

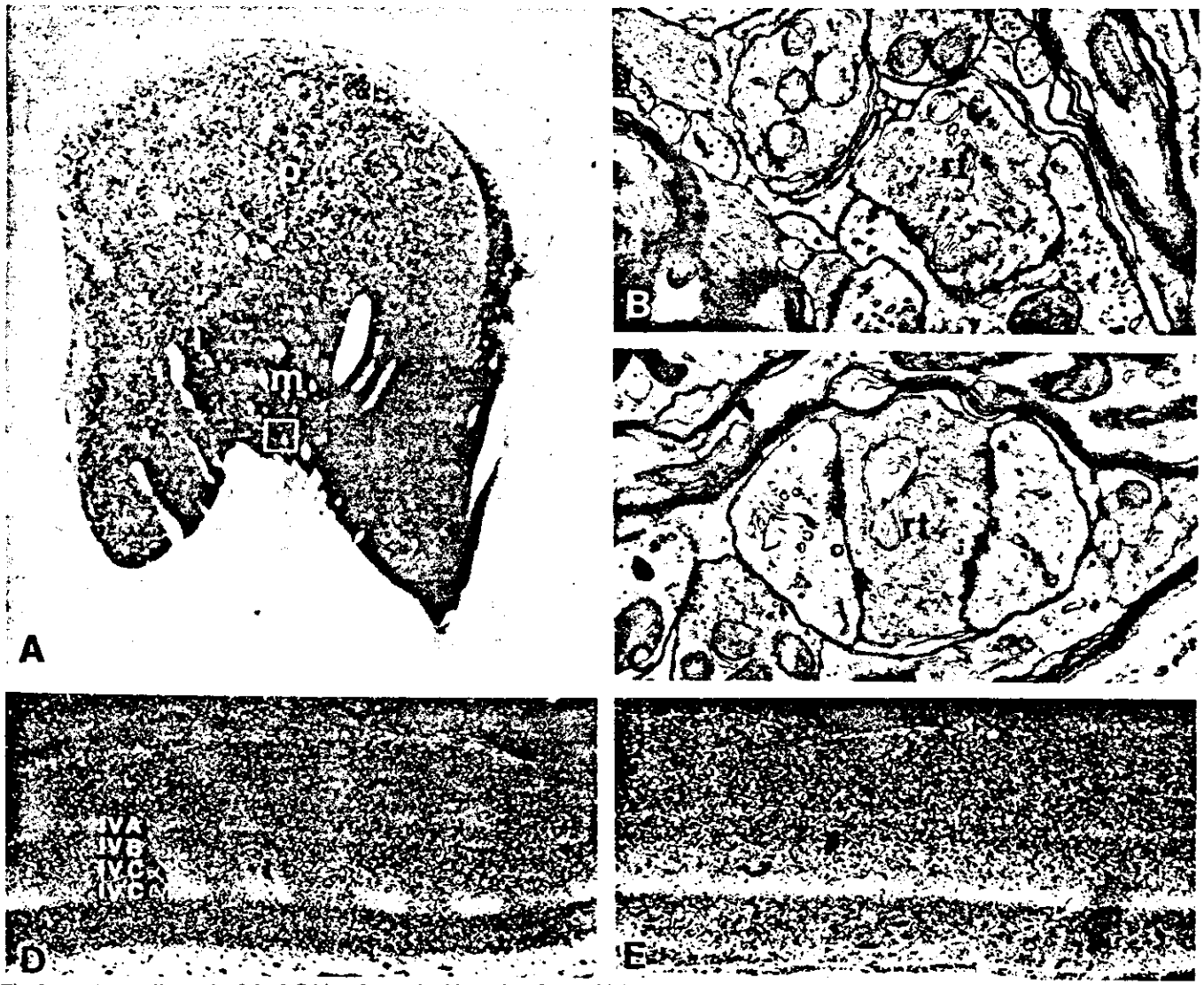

Fig. 2. (A) Autoradiograph of the LGd in a 2-month-old monkey from which one eye was removed at the second fetal month, showing the spread of radioactive retinal input over the entire nucleus. Although the magnocellular moiety (*m*) receives more dense input than the parvocellular (*p*), just as in the control monkeys (Fig. 1B), the layering pattern is not discernible. (B and C) Electron micrographs of retinal axon terminals (*rt*) in the left LGd in a monkey whose right eye was enucleated in the second fetal month. Such terminals are uniformly distributed and found even in the territories of presumptive layers 1 and 6 (indicated by rectangles in A), which normally receive input from the contralateral (removed) eye. (D) Dark-field autoradiograph of the primary visual cortex in a normal adult monkey. Transneuronally transported label is distributed in the form of alternating ocular dominance columns and over sublayers IVA, IVCα and IVCβ. (E) Autoradiogram of the primary visual cortex of a 2-month-old monkey from which one eye was removed at the second fetal month and the remaining eye injected with tracer 2 weeks before death. The label forms horizontal, uniform sheets without indication of ocular dominance columns, but segregated input into sublayers IVA, IVCα, and IVCβ is established.

though LGd neurons received morphologically normal synaptic input from the single remaining eye. This study further emphasizes that the binocular competition critical for the initial formation of the normal visual system does not require visual experience since it exercises its influence before birth. Finally, the dependence of normal development on prenatal binocular competition is selective; segregation of the LGd into magno- and parvocellular moieties and the laminar distribution of their terminals in the cerebral cortex developed normally in all experimental animals. This example of how an error in development of a single structure can alter distant but related structures in the complex primate brain may offer insight into various abnormalities of lamination or connections that occur in congenital malformations in humans.

PASKO RAKIC

Section of Neuroanatomy,
Yale University School of Medicine,
New Haven, Connecticut 06510

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12. The smaller size of the LGd in the monkeys enucleated at later gestational ages may be due to neuronal atrophy, loss of neurons, or both. This effect may be related to the higher dependence of already committed, more mature LGd neurons on the proper retinal input.
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