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Physiological and morphological effects of short and long term lid-suture on cells in the lateral geniculate nucleus of cats

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The University of North Carolina at Greensboro, 1986

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PHYSIOLOGICAL AND MORPHOLOGICAL EFFECTS OF SHORT AND LONG TERM LID-SUTURE ON CELLS IN THE LATERAL GENICULATE NUCLEUS OF CATS

by

Martha Grace MacAvoy

A Dissertation Submitted to
the Faculty of the Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

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Approved by

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APPROVAL PAGE

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This study addresses three main issues which have clearly arisen from the literature and when answered, bear directly on the role of experience on neural development. In order to address these issues, 22 cats were reared with varying durations of lid suture and LGNd cell encounter rates and cell body sizes were collected. Control data were collected from normal subjects.

Subjects reared with lid suture and from which data were collected before 17 months of age showed a reduction in the electrophysiological encounter rate for Y-cells and a reduction in average cell body size in geniculate laminae innervated by the deprived eye. Subjects from which data were collected at or after 17 months of age did not show a reduction in Y-cell encounter rate. In fact, it appears that X-cells were suppressed in the older subjects. Average cell body sizes in deprived geniculate laminae on the other hand, were smaller than normal. In these older subjects however, the relative difference between soma sizes in deprived and nondeprived laminae appears to decrease.

These results show that kitten-onset visual deprivation does not protect the deprived LGNd laminae from further adult-like (i.e. X-cell) losses. This suggests that

the effects of adult-onset deprivation paradigms do not depend upon an intact Y-cell system.

Also importantly, these results show that subject age may be an important variable in determining percentage of Y-cells encountered in deprived laminae following lid suture. This finding may account for some of the confusion in a literature which has not fully recognized the need for control of this variable. That is, subjects younger than 17 months should show a significant reduction in Y-cell encounter rate, whereas in subjects 17 months or older the Y-cell effect is obscured by a subsequent effect on the X-cell system.

Further, the morphological and physiological difference between nondeprived and deprived laminae is correlated within single subjects. That is, animals which showed a large reduction in percentage of Y-cells would be likely to show a large reduction in average cell body size as well.

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CHAPTER I

INTRODUCTION

The modern form of the debate concerning the role of sensory experience in development began almost 300 years ago with John Locke's "An Essay Concerning Human Understanding" (1690). William Molyneux had written Locke and posed the question of whether a blind man on recovering his sight would be able to distinguish a sphere from a cube by vision alone, without recourse to tactile stimulation. Both Locke and Molyneux determined that one would not be able to make the distinction. This basic question of the role that sensory experience plays in postnatal development was addressed repeatedly by philosophers in the eighteenth century who were divided into two camps, empiricists and nativists. The emiricists argued strongly that all ideas are derived from sensory experience. The infant mind was a "tabula rasa, a blank plate of wax upon which the moving finger of experience wrote the entire eventual content of consciousness and memory" (Walls, 1951, p. 57). Nativists, on the other hand held that certain ideas were innate.

Although the issue has been argued vigorously (Morgan, 1977; Pastore, 1971; Walls, 1951), little data have been available until quite recently. Consequently,

the questions have shifted to address the degree and form of interaction of genetic and environmental factors in development. The advent of electrophysiological methods within the last 15 years for the study of the functional properties of individual visual cells has made it possible to reformulate many of the old issues, now in more specific terms. Questions regarding the interaction of genetic and environmental factors have become important. In turn, this has led to a clearer understanding of the roles of genetic and experiential factors in the functional development of the neural systems that form the substrate of visual perception.

Using a developmental approach, there are two major ways to go about contributing to an understanding of the neurobiology of visual perception. One way is to document and describe the normal ontogenetic neuroanatomical and physiological changes which occur in the visual system in parallel with behavioral development. This approach has provided a great deal of insight into developmental processes. Certain methodological difficulties, however, have hampered the efficiency of this approach for describing visual development. For example, the ocular media in the immature cat are cloudy, making it difficult to study early postnatal visual physiology. A second way to approach the problem of understanding visual development is to study the response of the visual

system to experimental manipulations. Together with information gleaned from the more descriptive observations, this approach reveals the mechanisms involved in visual system development. Using this approach, not only can the effects of infantonset deprivations be explored, but the impact of adultonset manipulations can also be determined. The present set of experiments involve the use of this second approach, response of neural elements to manipulations of sensory input, for studying the developing as well as the developed animal.

Before describing these experiments however, it is necessary to provide a brief survey of the normal visual system, its development and its response to anomalous visual input. Information provided by behavioral studies of visual perceptual development will supplement the survey of physiological and morphological data. The first two sections will provide background information which will assist in the analysis and interpretation of results from studies described in the two subsequent sections. These latter two sections will examine experiments designed to study the degree to which the functional and structural development of individual neurons in the visual system can be modified by anomalous visual input. The effects of infantonset deprivations will be described first, followed by a review of the effects of adult-onset deprivations.

This survey focuses on development and function of the retinogeniculate system with emphasis on the dorsal lateral geniculate nucleus of the cat thalamus. I have elected to confine my survey (and the present study) to the LGNd for several reasons. First, since my principle efforts concern binocular interactions, it is necessary to concentrate on a structure where such interactions are possible. Second, while the physiology and anatomy of more central visual structures have received a great deal of attention, far more is known about visual processing at the level of the thalamus. Third, it is necessary to compare some of the results from the experiments in the present study to others gathered in this laboratory. Since Salinger and colleagues have confined their attention to the LGNd, then this has also been my focus. Finally, and perhaps most importantly, as will hopefully become clear, some controversy exists regarding the effects of certain manipulations on cells in the LGNd. One of the goals of the present experiment is to resolve this controversy.

Visual System Channels

The neural pathways from the retina via the dorsal lateral geniculate nucleus to the visual cortex in the cat are composed of at least three parallel channels. These have been arbitrarily labeled the X-, Y- and W-cell

systems and they remain largely segregated to the level of primary visual cortex (see Blake, 1979; Rodieck, 1979; Sherman, 1984; Sherman & Spear, 1982; Stone, Dreher & Leventhal, 1979, for reviews).

The W-cell system will be largely excluded from further consideration here for three primary reasons. First, it has become clear that W-cells are a heterogeneous class (Rodieck, 1979; Sur & Sherman, 1982). That is, the criteria for the classification of X- and Y-cells permit the accurate dichotomization of those cell types. Membership in the W-cell class, on the other hand, has traditionally been the fate of cells wich were clearly neither X nor Y (Dowling & Dubin, 1984). This practice has resulted in an amorphous class consisting of no fewer than six functionally distinct subtypes (Bishop, 1984; Cleland, Dubin, & Levick, 1971; Cleland & Levick, 1974a, b; Dubin & Cleland, 1977; Rodieck, 1979; Spear, Smith, & Williams, 1977). Second, while W-cells comprise a large fraction of the overall population of cells in the cat retina, the same is not true for primate retina (De Monasterio, 1981; Schiller & Malpeli, 1977). In fact, it has been suggested that W-cells are phylogenetically older and therefore may be a relic of a much more primitive visual system (Bishop, 1984; Rodieck, 1979; Stone, 1966). Third, and probably most important, far less is known about normal development in W-cells

than is known about both X- and Y-cells. This lack of background information would make it difficult to evaluate the role of W-cells in changes following sensory modifications. Therefore, the following brief description of visual system organization will concentrate on the X- and Y-cell systems with the W-cell system referred to only for completeness.

As will be seen, the X- and Y-cell channels are distinct from each other in their cellular and axonal morphology, receptive field characteristics, functional properties, distribution with respect to the visual field, and central projection patterns. Given these distinctions, it has been proposed that each channel relays information about different aspects of the environment (Bishop, 1984; Lennie, 1980; Sherman & Spear, 1982; Rowe & Stone, 1977; Stone, Dreher, & Leventhal, 1979). Furthermore, X- and Y-cells differ with regard to their ontogeny (Daniels, Pettigrew, & Norman, 1978; Norman, Pettigrew, & Daniels, 1977; Sur, Weller, & Sherman, 1984; Walsh, Polley, Hickey, & Guillery, 1983). These important distinctions will be elucidated in the following section. This background information is necessary in order to understand and explain differences in the responses of the X- and Y-cells to various alterations in the visual environment of the immature and mature organism.

Retina

Ganglion cell physiology. The concept of receptive field was first introduced by Adrian (1928) to describe observations of the spatial extent of skin surface served by individual afferent nerve fibers. It was much later before Hartline provided the first definition of the receptive field of single visual neurons as the area of retina that had to be illuminated in order to obtain a modulated response from a given fiber (Hartline, 1938, 1940). Later still, Kuffler (1953) provided the now classic description of the receptive-field organization for cat retinal ganglion cells. He described a concentrically arranged, antagonistic, center/surround receptive-field organization for each cell. Two types were noted: on-center and off-center cells. For on-center cells, the onset of light limited to a small retinal region (i.e., receptive-field center) raised the cells firing rate, as did cessation of a bright annulus surrounding this region (i.e., receptive-field surround). For off-center cells, the reverse was true. Thus, the receptive fields of the cells described by Kuffler (1953) display no stimulus selectivity other than that for the position and contrast of targets falling on the retina.

Subsequent research has shown that retinal ganglion cells can be further classified along dimensions other than on- or off-center characteristics. A germinal

study in the development of a comparable understanding in mammals was EnrothCugell and Robson's (1966) analysis of the cat retina, in which they distinguished two types of ganglion cells, 'Y-' and 'X-'cells. While attempting to apply Fourier methods to individual ganglion cells, Enroth-Cugell and Robson (1966) noted that retinal ganglion cells could be divided into two types which they termed X and Y based on their responses to drifting sinusoidal gratings at the highest spatial frequency capable of eliciting a response. The X-cells always showed response modulation at the drift frequency, while Y-cells showed an unmodulated increase in mean discharge rate, that is X-cell responses were linear while the Y-cell responses were not. Enroth-Cugell and Robson (1966) also noted that these two cell types differed systematically in other ways which suggested a functional distinction. Y-cells had relatively large receptive fields, and were relatively uncommon at the area centralis. By contrast, X-cells had relatively small receptive fields, and were common at the area centralis. Others have extended the list of criteria which distinguish X- from Y-cells. The axons of Y- and X-cells have been shown to conduct action potentials at differing average rates which correspond to the two conduction velocity groupings which had much earlier been recognized in cat optic nerve (Bishop & Clare, 1955; Bishop, Clare, & Landau, 1969; Bishop,

Jeremy, & Lance, 1953; Bishop & McLeod, 1954). Specifically, Y-cells have been shown to have fast conducting (30-40 m/s) and X-cells slow conducting (18-25 m/s) axons (Cleland et al., 1971; Fukada, 1971). The X/Y distinction has since been investigated intensively and related to a wide range of receptive field properties (Cleland et al., 1971; Cleland, Harding, & Tulunay-Keesey, 1979; Cleland, Levick, & Sanderson, 1973; Hochstein & Shapley, 1976a, b; Saito, Shimahara, & Fukuda, 1971; Sur & Sherman, 1982).

More recent work has suggested that the linear/non-linear distinction may be of importance in position sensitivity because X-cell responses to stimuli of all spatial frequencies are dominated by the fundamental component. That is, an X-cell can always signal the presence of a stimulus as well as its absolute position within the receptive field (Sur & Sherman, 1984). In contrast, Y-cell responses are dominated by the linear component only at lower spatial frequencies. At higher ones, Y-cell responses are dominated by non-linear components that are spatially phase independent (Hochstein & Shapley, 1976a, b). Therefore, while these non-linear responses of a Y-cell can clearly signal the presence of a stimulus with considerable reliability, they cannot accurately signal the absolute position of that stimulus within the receptive field. Nonetheless, it is possible that

at higher spatial frequencies these non-linear Y-cell responses are quite sensitive to slight shifts of target position even though they cannot signal position (Sur & Sherman, 1984).

X-cells tend to respond to appropriate standing-contrast targets (a bright spot in the center for an on-center cell, a dark spot for an off-center cell) with a much more tonic or sustained response than do Y-cells (Cleland et al., 1971; Hoffmann, Stone, & Sherman, 1972; Saito et al., 1971). Y-cells cease responding to such a stimulus within a few seconds, whereas X-cells respond for 20 seconds or more. X-cells usually respond to higher spatial frequencies and thus tend to have better spatial resolution than Y-cells (Cleland et al., 1979; So & Shapley, 1979). Finally, Y-cells respond to faster target motions than do X-cells (Cleland et al., 1971).

It is interesting to consider these response parameters in the context of recent hypotheses regarding the functional significance of the X- and Y-cell pathways. Although several models have been proposed (Ikeda & Wright, 1972; Lehmkuhle, Kratz, Mangel, & Sherman, 1980, 1982; Lennie, 1980; Stone et al., 1979; Troy, 1983) one stands out as more consistent with the current data base (Lehmkuhle 1980a, 1982; reviewed in Sherman, 1984). This hypothesis suggests that the Y-cell pathway, with its unique sensitivity to the lower spatial frequencies, is responsible for

the basic spatial analysis of visual patterns, whereas the X-cell pathway, with its sensitivity to higher spatial frequencies, raises acuity by adding spatial detail. The X-cell pathway may also be crucial to other roles, such as stereopsis (Bishop, 1984; Sur & Sherman, 1984), and the Y-cell pathway, with its insensitivity to phase angle at higher spatial frequencies, could plausibly serve as a sensitive motion alerting system (Sur & Sherman, 1984). X-cells exhibit better absolute position sensitivity, but only for the higher spatial frequencies. This response pattern seems suited for extracting the maximal spatial information from the higher frequencies in order to maximize acuity (Sur & Sherman, 1984).

Ganglion cell morphology. Retinal ganglion cells are the output cells of the retina. Their cell bodies and dendritic trees lie on the retina. Using the Golgi technique, Boycott and Wassle (1974) described separate classes of retinal ganglion cells based on differences in cell body size and dendritic morphology. Of these, the alpha type were shown to have the largest somata and the largest dendritic trees. The beta type had smaller somata than alpha cells within any given retinal area, and had the smallest dendritic tree of any class. Ganglion cells have their peak density in central retina, and decline in density monotonically toward the periphery (Hughes, 1975; Hughes, 1981; Stone, 1965; Stone, 1978).

As might be expected if these morphological classes have functional significance, the distribution of each class mirrors the total density map of all retinal ganglion cells. That is, the entire visual world is mapped by each cell class.

Morphological-physiological correlation. Data primarily from Wassle and colleagues (Boycott & Wassle, 1974; Cleland, Levick & Wassle, 1975; Illing & Wassle, 1981; Peichl & Wassle, 1981; Wassle, Levick, & Cleland, 1975) suggest that the physiologically identified Y-cells are alpha cells and X-cells are beta cells. However, the methods used in these studies to establish these relationships have been indirect. More recently it has become possible to perform a direct structure-function analysis on retinal ganglion cells. This has been accomplished using a technique which combines the methods of intracellar and extracellular electrophysiological characterization of a neuron followed by intracellular injection of horseradish peroxidase. Histochemical processing for horseradish peroxidase can then provide a detailed Golgi-like morphological view of the physiologically identified cells, and thus, a direct comparison could be made between the structure and function of individual neurons (Fukuda, Hsiao, Watanabe, & Ito, 1984; Stanford & Sherman, 1984). In both reports, cells physiologically identified as X-cells were found to

have beta morphology and cells identified as Y-cells had alpha morphology.

Central projections. Axons of retinal ganglion cells converge to form the optic disk and exit from the eye as the optic nerve. Ganglion cell axons which lie nasal to the area centralis decussate at the optic chiasm and enter the contralateral optic tract, while those which lie on the temporal side of the area centralis do not cross and thus contribute to the ipsilateral optic tract (Kirk, Levick, & Cleland, 1976; Stone & Fukuda, 1974). Retinal ganglion cells send direct projections to the suprachiasmatic nuclei of the hypothalamus (Berman & Jones, 1977), the dorsal and lateral geniculate nuclei (Berman & Jones, 1977; Hayhow, 1958; Hollander & Sanides, 1976; Mize & Horner, 1984), medial interlaminar nuclei (Berman & Jones, 1977; Guillery, 1970; Hayhow, 1958; Kinston, Vadas, & Bishop, 1969; Mize & Horner, 1984), perigeniculate nuclei (Berman & Jones, 1977; Laties & Sprague, 1966; Sanderson, 1974), pulvinar (Berman & Jones, 1977), nuclei of the optic tract and accessory optic system (Berman & Jones, 1977; Hayhow, 1959; Hayhow, Webb, & Jervie, 1960), olivary nuclei (Berman and Jones, 1977), pretectum (Berman & Jones, 1977; Hoffmann & Schoppmann, 1975; Laties & Sprague, 1966), and superior colliculus (Berman & Jones, 1977; Graybiel, 1975, 1976; Harting & Guillery, 1976; Kanaseki & Sprague, 1974).

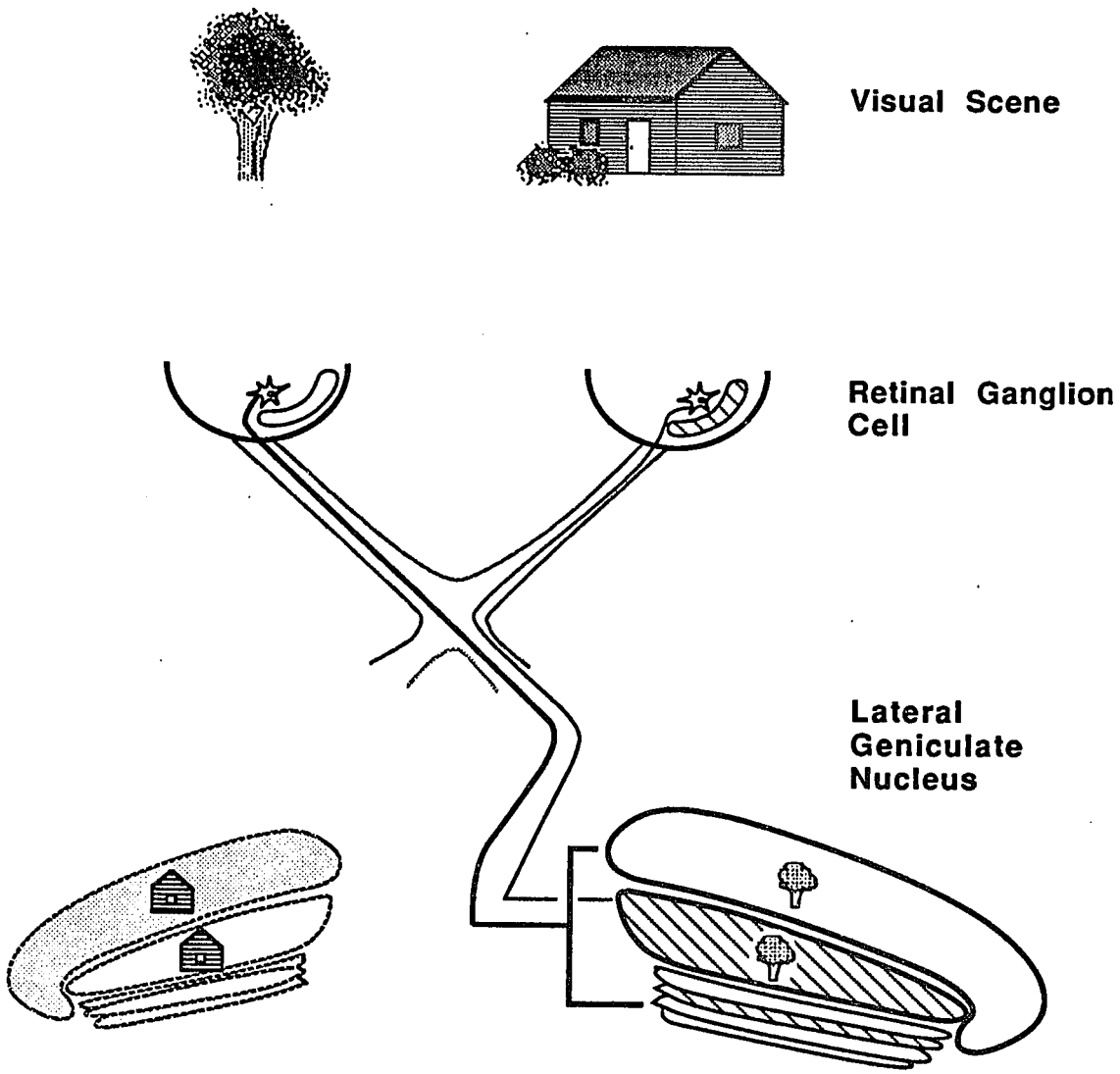
Dorsal Lateral Geniculate Nucleus (LGNd)

Figure 1 is a simple version of the cat's retino-geniculate pathway. A coronal view of the cat LGNd is represented schematically in this figure. Six laminae have been recognized in the laminated portion of the cat lateral geniculate nucleus [(LGNd)(Rioch, 1929)]. These have been labeled A, A1, C, C1, C2 and C3 by Hickey and Guillery (1974), the first five of which receive retinal projections (Hickey & Guillery, 1974). These laminae are stacked in retinotopic register so that a line normal to the external surface of lamina A passing through them represents the same point in visual space viewed from opposite eyes (Bishop, Kozak, Levick, & Vakkur, 1962; Kaas, Guillery & Allman, 1972; Sanderson, 1971a, b). That is, the eye of origin of the retinal axons innervating these laminae segregate their outputs such that the dorsal most layer (lamina A) is innervated by cells lying in the contralateral retina, while the next layer, lamina A1, is innervated by cells lying in the ipsilateral retina. The innervation pattern continues in this alternate contralateral- ipsilateral pattern through layers C, C1 and C2, so that for either LGNd, laminae A, C, and C2 receive contralateral afferents, while laminae A1 and C1 receive ipsilateral afferents.

Although the LGNd is comprised of six laminae,

Figure 1. A schematic version of the cat's retino-geniculate pathway. This figure also shows how the visual world is represented in the retina and lateral geniculate nucleus.

Figure 1


Visual Scene
Retinal Ganglion Cell
Lateral Geniculate Nucleus

only layers A and A1 will be considered here, for three main reasons. First, layers A and A1 have been considered to be a matched pair phylogenetically distinct from the C laminae (Kaas et al., 1972; Sherman & Spear, 1982). The A and A1 laminae of both geniculates are about the same size and together they receive information from the entire visual field. Secondly, the A and A1 laminae receive innervation from only X- and Y-cells (Sur & Sherman, 1982; Wilson, Rowe, & Stone, 1976; Wilson & Stone, 1975). On the other hand, the C laminae have been viewed as distinct from the A laminae because they receive a strong W-cell input and have a pattern of central connections which is quite different from the A laminae (Bullier & Henry, 1979a, b, c; Garey & Blakemore, 1977; Garey, Jones, & Powell, 1968; Geisert, 1980; Lin & Sherman, 1978; Sur, Hockfield, MacAvoy, Garraghty, Kritzer, & McKay, 1984). Finally, largely due to these first two reasons, laminae A and A1 have been studied in great detail and therefore most of the information regarding LGNd structure and function includes only these laminae.

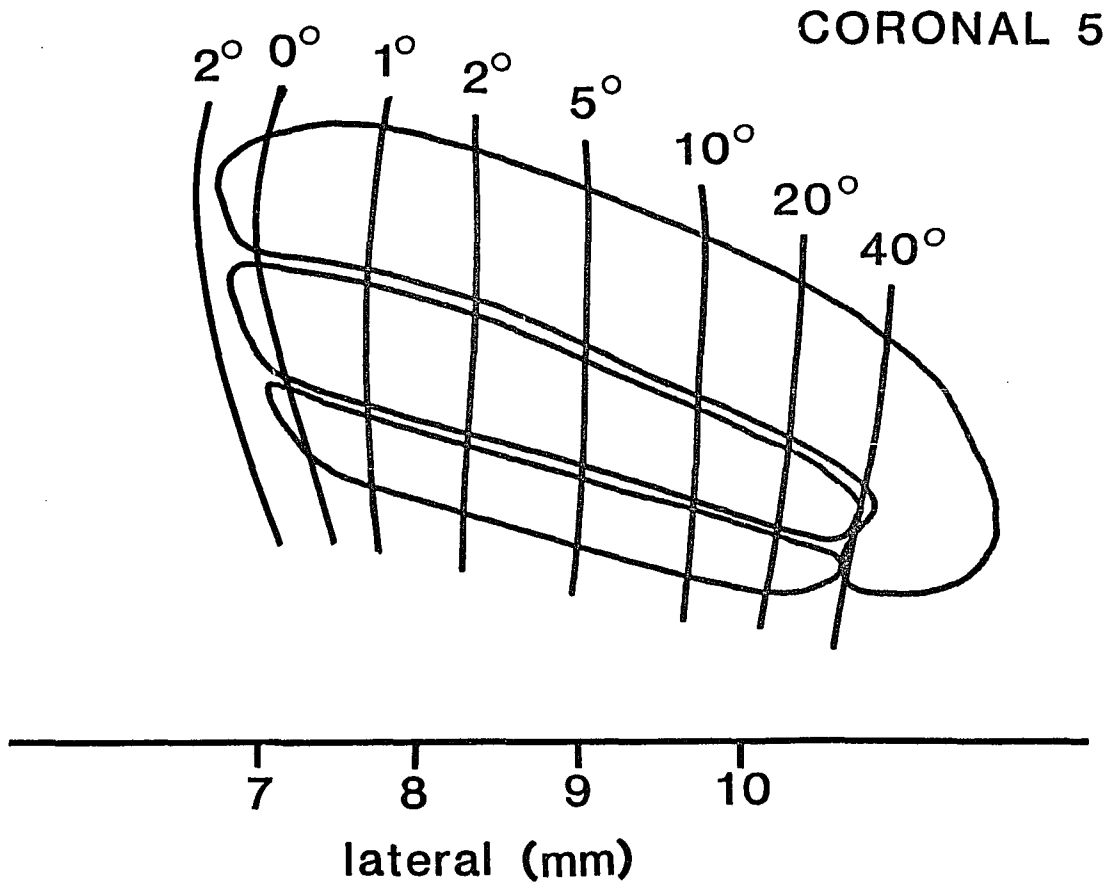
Binocular and monocular segments. In addition to the obvious lamination, the LGNd is also organized with respect to the visual field represention. Each geniculate neuron has a small receptive field limited in visual space, and neighboring neurons map neighboring

spatial coordinates. As a consequence, an orderly, precise point-to-point map of visual space exists in the LGNd (Kaas et al., 1972; Sanderson, 1971a, b): lateral (or medial) displacements in the nucleus yield more peripheral (or central) visual receptive field locations in the contralateral hemifield, and the medial edge of the nucleus represents the vertical meridian of visual field; rostral (or caudal) displacements yield more inferior (or superior) visual positions. Figure 2 is a coronal view of the LGNd with conventions as in Figure 1. The superimposed vertical lines represent areas of the visual field in which the underlying cells of the LGNd have their receptive fields (adapted from Sanderson, 1971b). The binocular segment includes all of lamina A1 and the medial three fourths of lamina A and represents the central visual field which is seen by both eyes (Bishop et al., 1962; Guillery, 1972; Guillery & Stelzner, 1970; Kaas et al., 1972; Sanderson, 1971a, b; Sherman, 1973). The monocular segment is that part of lamina A which maps the extreme peripheral crescent of the visual field which can be viewed by only one eye. For example, cells of the monocular segment for the left LGNd would have receptive fields from 45-90o to the right of midline (Guillery, 1972; Guillery & Stelzner, 1970; Sherman, 1973) and would be found in the lateral portion of lamina A, extending beyond lamina

Figure 2. Coronal view of the lateral geniculate nucleus with superimposed isoazimuth lines. These lines represent portions of the visual world which correspond to the receptive fields of underlying geniculate areas.

Figure 2

Pattern of Isoazimuth Lines



A1. The distinction between binocular and monocular segments becomes functionally important as one recognizes that the opportunity for binocular interactions in the LGNd should be confined by these structural features to the regions of the LGNd which are in the binocular segment (Sherman, 1973; Sherman & Spear, 1984).

LGNd cell physiology. Like the ganglion cells from which they derive their inputs, geniculate neurons in the cat possess receptive fields which are concentrically organized, with both ON-center and OFF-center types (Hubel & Wiesel, 1961). Moreover, the diameters of the receptive field centers of LGNd cells are on the same order of magnitude as ganglion cells; field sizes increase with retinal eccentricity (Hoffmann et al., 1972; Hubel & Wiesel, 1961). There are, however, some notable differences between ganglion cell and geniculate cell fields. At the geniculate level, the surround mechanism exerts a greater inhibitory influence on the center, in comparison to surrounds at the retinal level, thus enhancing the sensitivity of geniculate neurons to luminance gradients (Hammond, 1972; Hubel & Wiesel, 1961). Moreover, the surround portion of the geniculate field is responsive even at scotopic levels well below those at which the effects of ganglion cell surrounds disappear (Hammond, 1973; Maffei & Fiorentini, 1972). Unlike the retina, the LGNd contains some cells which

can be influenced via either eye, such that the cell is excited by stimulation of one eye and inhibited through the other (e.g., Sanderson, Bishop, & Darian-Smith, 1971). In view of the strict segregation of left- and right-eye afferents to the different laminae, it seems likely that interneurons supply the connections for these binocular inhibitory interactions (Dubin & Cleland, 1977; see Schroeder, 1985 for review).

By recording simultaneously from a geniculate neuron and the ganglion cell(s) providing the excitatory input, several investigators have demonstrated that most LGNd neurons are innervated by just a few optic fibers and in some cases by only a single fiber (Cleland et al., 1971; Hammond, 1973; Hoffmann et al., 1972; Singer & Creutzfeldt, 1970). These simultaneous recordings also have demonstrated two important functional properties of the excitatory connections between retinal fibers and LGNd cells. First, geniculate cells with ON-center fields receive excitatory input only from ON-center ganglion cells, and OFF-center geniculate cells are excited just by OFF-center ganglion cells (Cleland et al., 1971). Second, the X/Y grouping described for retinal cells is preserved at the LGNd. That is, while a small degree of X/Y convergence may occur (Cleland et al., 1971; Cleland, Levick, Morstyn, & Wagner, 1976; So & Shapley, 1979; Wilson et al., 1976), in the vast

majority of cases X-type retinal cells innervate only X-type geniculate neurons and Y-retinal cells only Y-geniculate neurons (Cleland et al., 1971; Hoffmann et al., 1972). In the adult, LGNd X-cells are subject to greater inhibitory influences than the Y-cells (Berardi & Morrone, 1984). Like the retinal X-cells the LGNd X-cells have a slower conduction velocity (Cleland et al., 1971; Cleland et al., 1976; Eysel, Grusser, & Hoffmann, 1979; Fukuda & Saito, 1972; Garraghty, 1985; Hoffmann & Stone, 1971; Hoffmann et al., 1972; Wilson et al., 1976; Wilson & Stone, 1975) and a smaller receptive field size than LGNd Y-cells (Bullier & Norton, 1979a, b; Hoffmann et al., 1972; Wilson et al., 1976). Like their retinal counterparts, LGNd X-cells sum light linearly across their receptive fields (Bullier & Norton, 1979a, b), their response to a stimulus is sustained (Bullier & Norton, 1979a, b; Cleland et al., 1971; Hoffmann et al., 1972) and they do not respond well to stimuli of high temporal frequencies (Hoffmann et al., 1972; Lehmkuhle, Kratz et al., 1980; So & Shapley, 1981). LGNd Y-cells on the other hand sum light nonlinearly (Bullier & Norton, 1979a, b), respond with a transient burst to photic stimulation and have a good response to high temporal frequencies (Cleland et al., 1971; Hoffmann et al., 1972; Lehmkuhle et al., 1980; So & Shapley, 1981).

LGNd cell morphology. Guillery (1966) used Golgi-impregnation techniques to provide the first systematic discription of the morphology of neurons in the cat lateral geniculate nucleus. As was the case for retinal ganglion cells, intracellular recording and horseradish peroxidase iontophoresis have been subsequently used to define structure/function relationships for single LGNd cells. These results (Friedlander, Lin & Sherman, 1979; Friedlander, Lin, Stanford, & Sherman, 1981; Stanford, Friedlander, & Sherman, 1981) combined with those reported by Guillery (1966) suggest that Y-cells are the largest with thick, cruciate dendrites which typically cross laminar boundries and are arranged in a spherical fashion. They have dendritic appendages that tend to be simple, spinelike structures. X-cells are intermediate in size, with thin, sinuous dendrites vertically oriented along the projection lines in the LGNd. These appendages are always restricted to the same lamina as the soma. X-cells can also be small, with thin, tortuous dendrites which again are contained within a single lamina, with many complex dendritic appendages.

Central projections. X- and Y- geniculate cells are also distinguishable on the basis of the pattern of their cortical projections (Bullier & Henry, 1979a, b, c; Garey & Blakemore, 1977; Garey et al., 1968; Geisert, 1980; Lin & Sherman, 1978; Sur, Hockfield, MacAvoy,

Garraghty, Kritzer, & McKay, 1984). X-cells project primarily to cortical area 17, or primary visual cortex with little or no input to area 18; whereas Y-cells project to both areas 17 and 18 (Humphrey, Sur, Uhlrich, & Sherman, 1985). Furthermore, X- and Y- geniculocortical axons have a strong tendency to terminate in different cortical sublaminae. Geniculocortical X-axons terminate preferentially in lower layer 4 (4b), while Y-axons tend to arborize in upper layer 4 (4a) and layer 3 (Rodieck, 1979; Sherman & Spear, 1982).

Parallel pathways. In summary, X- and Y-cell classes in the retina and the LGNd can be clearly distinguished on the basis of cellular morphology and physiology, and pattern of central projections. The bulk of evidence supports the idea, therefore, that X- and Y-cells are two distinct classes of cells and do not represent a continuum. In fact it has been strongly argued that the X- and Y-cells form separate streams from retina to visual cortex (Bishop, 1984; Bullier & Henry, 1979a, b, c; Harvey, 1980a, b; Hoffmann & Stone, 1971; Rodieck, 1979; Rowe & Stone, 1977; Stone, 1972; Stone & Dreher, 1973; Stone et al., 1979).

The distinction between X- and Y-cells becomes especially important when discussing the effects of various sensory modifications on the developing or mature nervous system. This is the case because the bulk of

evidence suggests that these two classes of cells can also be distinguished on the basis of their response to visual deprivation. The perceptual development of the organism as well as the distinct anatomical and physiological development of the X- and Y-cells lends support to the idea that these are two distinct classes of neurons. Additionally, in order to interpret reliably data reported from deprivation studies, it is necessary to have some background information on these courses of development.

Development of Visual Processes

Development of visual perception. The normal development of two basic aspects of visual perception will be described here: (1) resolution of spatial detail, and (2) binocular depth perception, or stereopsis. The nature of these processes will then be discussed in terms of how they relate to the X- and Y-cell systems as well as to visual deprivation paradigms. It is possible to obtain behavioral estimates of acuity in kittens from the age of about 4 weeks (Giffin & Mitchell, 1978; Mitchell, Giffen, Wilkinson, Adderson, & Smith, 1976). Resolution improves gradually from 30 days postnatal (approximately .75 cycles/degree) to approach adult values (5-7 cycles/degree) at around the end of the fourth month. The rather gradual development of visual

perception in cats suggests that the neural connectivity underlying these tasks may require environmental stimulation, unlike that possibly of the chicken, which attains peak acuity within 48 hours of hatching (Over & Moore, 1981). However, in addition to neural connectivity, there are three prominent peripheral processes that could, in principle, contribute to the increase in spatial resolution observed in the immediate postnatal period: (1) improvement on the optical transmission properties of the eye, (2) rescaling of the retinal map of visual space, and (3) changes in retinal receptor mosaic.

Improvement in the optical transmission properties of the eye. The development of the perceptual capacity to resolve spatial detail is ultimately dependent upon the optical development of the eye. The cloudy appearance of the optical media of kittens during the first two weeks of postnatal life suggests that optical image quality may serve as the major constraint on visual acuity during this period. However, image quality is surprisingly good (Bonds & Freeman, 1978; Derrington, 1978) and considerably better than measured acuity (Mitchell et al., 1976). Thus it appears that optical factors do not impose a major constraint on acuity in the kitten.

Rescaling of the retinal map of visual space. Rescaling may be particularly relevant in the case of the kitten eye, the axial dimensions of which almost

double from birth to 6 months of age (Thorn, Gollender, & Erickson, 1976). The presence of rescaling is revealed by changes with age of two retinal landmarks. Such measurements have shown that some rescaling occurs (Olson & Freeman, 1980). From the time when behavioral acuity measurements are first possible (30 days) to the time at which acuity has stabilized (4-5 months), however, this angle changes less than 30%. The improvement in acuity over this period is almost an order of magnitude (Mitchell et al., 1976). Thus, although some improvement in the acuity of the kitten may be attributed to growth of the eye itself, the extent of this contribution is not substantial.

Changes in retinal organization. The anatomical organization of the retina of the cat is incomplete at birth (Donovan, 1966; Johns, Rusoff, & Dubin, 1979; Rusoff, 1979; Stone, Rapaport, Williams, & Chalupa, 1982; Tucker, 1978). A postnatal increase in ganglion cell density and size occurs which could contribute to an increase in spatial resolution (Mitchell & Timney, 1984). Although these changes must contribute to the improvement in acuity observed after birth, the magnitude of these changes is too small to account for much of the measured improvement in visual resolution (Tucker, 1978).

Changes in neural organization. The ability to

discriminate depth under natural viewing conditions depends on several cues, most of which are monocular but some are exclusively binocular. By far the most prominent mechanism of depth perception is stereopsis, which relies on retinal disparity cues (Wheatstone, 1838). The majority of early studies of depth perception in young animals were made in relatively natural situations with many cues available to determine whether immature organisms could perceive depth and react in a spatially appropriate manner. The visual cliff, developed by Walk and colleagues (Walk, 1966; Walk & Gibson, 1961) is perhaps the best known of these, and it has proved valuable in demonstrating that infants of a number of species can discriminate large differences in depth at an early age. Thus, it is important to focus attention on the development of stereopsis, a binocular mechanism of depth perception whose neural basis is recognized and one that is known to be disrupted by anomalous early visual input.

Possibly because of a lack of suitable techniques, little is known about the development of stereopsis in species other than humans. Using a modified jump stand (Mitchell, Kaye, & Timney, 1979), it has been possible to determine the ability of kittens to discriminate small differences in depth between two surfaces. When young kittens are tested under these conditions, they

show a marked binocular superiority by the age of 30-35 days, suggesting they possess stereopsis (Timney, 1981). Thereafter depth thresholds improve slowly, reaching adult levels at about 70 days. The early stage of depth perception coincides with the time course of fine tuning of binocular cells to retinal disparity in the visual cortex (Pettigrew, 1974).

Growth-related changes in the dimension of an individual eye could also limit stereoacuity. But more importantly, stereoacuity is also influenced by the growth of the head. This has the effect of altering the depth value associated with a constant retinal disparity. The inter-pupillary distance of the kitten, for example, increases from about 2 cm at 4 weeks of age to almost 4 cm in the adult (Mitchell & Timney, 1984). This means that the retinal disparity corresponding to a given separation between two targets increases by approximately a factor of two as the kitten grows. Even without improvement in neural tuning, discrimination of real separations in depth should improve by that amount. It is clear from the data presented here, however, that depth thresholds improve considerably more.

A key component of the system of binocular correspondence is a theoretical surface in visual space called the horopter. The horopter is defined as a spherical surface passing through the point of fixation that is

everywhere equidistant from the two retinae and images from which are therefore cast on corresponding points of the two retinae (Ogle, 1932, 1950, 1962; Wheatstone, 1838). As such it represents the locus of points in space around which stereoscopic processing is possible. Recent neurophysiological determinations of the zero meridian of the azimuth for the two eyes of the cat and of the owl (Cooper & Pettigrew, 1979) indicate that they are extorted with respect to each other in the same way as the corresponding meridians of the human retina. This means that the locus of points in space whose images fall simultaneously on these two meridians (referred to as the vertical horopter) is a line tilted in the sagittal plane passing through the fixation point and which slopes away at the top. It has long been recognized that the vertical horopter of the human passes through the feet (Cogan, 1979; Smith, 1981), and it now appears that a similar situation exists in the cat and owl (Cooper & Pettigrew, 1979). On the assumption that the vertical horopter must pass through the feet throughout development, then some plasticity of binocular connections is demanded throughout the time both height and interocular separation are changing. This situation requires that some plasticity be retained until physical growth of the organism has ceased. Since in the cat, physical development (consequently height and interpupillary

distance) may continue until around sixteen months of age (Sobel, 1976), neurons responsible for stereopsis should remain relatively mutable until this age. Thus even though measurements of stereopsis may reach adult levels before sixteen months, the neural substrate of stereopsis must remain plastic until adult size is attained.

In summary, although each of the mentioned peripheral factors makes some contribution to the gradual improvement in visual performance observed in the first few months of postnatal life, the major source of the improvement must be attributed to changes in neural organization and/or connectivity central to the retina. Consequently we consider next the normal development of the visual pathway.

Development of ganglion cells. During histogenesis, the ganglion cells are produced in broad waves, which overlap temporally. Cells are produced first for central then for peripheral retina (Rapaport & Stone, 1983; Stone et al., 1982; Walsh et al., 1983) and medium sized cells (presumably X-cells) are produced before the largest cells (Y-cells).

The order of ganglion cell production found in the cat retina is closely related to fiber order in the optic tract (Walsh et al., 1983). Thus in the optic tract, medium caliber axons (presumably from X-cells; Fukuda et al., 1984; Hsiao, Watanabe, & Fukuda, 1984)

lie in the center of the fiber bundle and represent the oldest ganglion cells. Large caliber axons (presumably from Y-cells; Fukuda et al., 1984; Hsiao et al., 1984) lie nearer the pia and a dense group of the finest axons are in a sub-pial position.

By the time kittens reach 3-4 weeks of age, most optic tract axons can already be identified physiologically and morphologically as members of the X- or Y-cell class. X-cell axons innervate the LGNd before Y-cell axons do (Daniels et al., 1978; Torrealba, Guillery, Eysel, Polley, & Mason, 1982). X-cell terminal fields in the LGNd are wider at 3-4 weeks than they are in adults, (Sur, Weller, & Sherman, 1984) while Y-cell terminal fields at this age are narrower than in adults (Friedlander, Martin, & Vahle-Hinz, 1985; Sur, Weller & Sherman, 1984). During the second and third postnatal months X-cell terminal arbors progressively contract, while Y-arbors expand, so that by 12 weeks the adult pattern is seen (Sur, Weller, & Sherman, 1984). Therefore, by a process analogous to that suggested for other developing neural systems (Purves & Lichtman, 1980), X-cells may initially have exuberant terminations which are altered by the subsequent input of the Y-cells (Garraghty, 1985; Garraghty, Sur, & Sherman, 1986; Sherman, 1985).

Development of LGNd cells. Daniels et al. (1978) found that even in 6- to 13- day old kittens, cells

were segregated into laminae according to eye dominance and that the normal topographic representation of the visual field was already established. The response properties of the neurons, however, were grossly abnormal and cell body sizes have been reported to be small (Hickey, 1980; Kalil, 1978b, 1980) compared with the adult. As was the case for retinal ganglion cells, the X- and Y-cell systems differ in their rate of development at the level of the LGNd. It is currently well established that most X-cells in the LGNd mature functionally before Y-cells (Norman et al., 1977; Daniels et al., 1978; Ikeda & Tremain, 1978; Berardi & Morrone, 1984). Kalil (1980) has characterized this difference by documenting the time course of morphological development for LGNd X- and Y-cells. In the newborn kitten, geniculate neurons are clustered tightly about the population mean of average cell body sizes, but a broadening of the distribution is evident as early as three days postnatal. By 14 days there is a noticeable increase in the number of medium sized (presumably X) neurons. During the next two weeks the gain in medium-sized cells is dramatic, and is accompanied by the emergence of a modest number of large cells (presumably Y). Between 28 and 56 days postnatal it is the large cell group that undergoes the most striking change. The number of large cells approximately doubles during the second postnatal month,

and the resulting proportions of medium and large cells in the LGNd of the 8-week old kitten are nearly identical to those in the adult (Kalil, 1980).

Measurements of the development of spatial resolution of LGNd cells have also been taken. These measurements are made by determining the resolution of X-cells for gratings drifted across their receptive fields. In kittens, the resolution of LGNd X-cells (defined as the highest spatial frequency grating that could elicit a modulated discharge) in the vicinity of the area centralis is very low at 3 weeks and slowly attains adult levels by 16 weeks (Ikeda & Tremain, 1978). This time course is comparable to the behavioral improvement of visual acuity (Giffin & Mitchell, 1978).

In summary, from birth until about four months of age, the retina and LGNd of the kitten undergo rapid development. Studies of this process have generally focused on one or more of three main aspects of development; perceptual, anatomical, and physiological. Perceptually, the kittens visual acuity has been shown to reach adult levels by about four months of age. Stereopsis, on the other hand, reaches adult levels by about nine weeks, but due to changing height and interocular distance, the neural substrate must remain in a mutable state until about sixteen months, at which time the cat is fully grown. Most of what is known concerning retinal

and LGNd cell development suggests that X-cells precede Y-cells in reaching maturity, both structurally and functionally. This neural development temporally coincides with visual perceptual development, reaching mature levels by about the end of the fourth postnatal month. Many attempts to elucidate the mechanism(s) involved in this normal developmental sequence have involved altering the visual environment of immature organisms and assessing the effects on the visual nervous system.

Neurological Effects of Altering the Visual Input of Immature Organisms

Since the visual system of the kitten is still undergoing rapid development, it would not be surprising to find that experimental alterations in the visual environment of juveniles have some effect on the function and growth of visual neural centers. Many experimental paradigms have been used to assess the extent to which the structure and function of the developing nervous system can be altered by modifications in sensory experience. Perhaps the most widely used strategy has involved depriving an animal of patterned visual input through one or both eyes by means of lid suture. Wiesel and Hubel (1963) pioneered this line of research with a series of experiments in which they compared receptive field properties of single visual neurons in cats reared

from birth with visual deprivation with those in normal cats. Since neurons in the LGNd of lid sutured cats retained the normal concentric, on-off pattern of their receptive fields, Wiesel and Hubel (1963) concluded that early visual deprivation had little, if any physiological effect in the LGNd. Other early studies replicated the observations that the physiological effects of visual deprivation in the LGNd were subtle at best (Hamasaki, Rackensperger, & Vesper, 1972; Sherman & Sanderson, 1972).

The formulation by Enroth-Cugell and Robson (1966) of the X and Y retinal ganglion cell dichotomy opened the door for additional assessments of the physiological effects of deprivation in the LGNd. After showing that geniculate cells could also be classified as X or Y (Hoffmann et al., 1972), Sherman, Hoffmann and Stone (1972) found that even though the receptive fields of cells in the deprived laminae retained their concentric center-surround organization as described by Wiesel and Hubel (1963), both monocular and binocular lid suture led to a marked reduction in the proportion of Y-cells sampled. With binocular lid suture, this selective loss of Y-cells was reported to be present throughout the monocular and binocular segments of the LGNd. The loss of Y-cells after monocular lid suture, on the other hand, was found to be largely confined to the binocular

portion of the LGNd; Y-cell encounter rate in the monocular segment of the deprived lamina was found to be more nearly normal (Sherman et al., 1972). The basic finding of a selective loss of Y-cells after early visual deprivation has been widely replicated (Eysel et al., 1979; Garraghty, Salinger, & Hickey, 1983; Geisert et al., 1980; Kratz, Webb, & Sherman, 1978b; Mower, Berry, Burchfiel, & Duffy, 1981; Salinger, MacAvoy, & Garraghty, 1978; Sherman, Guillery, Kaas, & Sherman, 1975; Sherman & Wilson, 1981; Sherman, Wilson & Guillery, 1975; Zetlan, Spear, & Geisert, 1981).

The morphological effects on cells in the LGNd after lid suture have also been found to be severe. Eyelid suture beginning in early kittenhood leads to a failure of normal growth of cells in the laminae receiving projections from the deprived retina (Dursteler, Garey, & Movshon, 1976; Friedlander, Stanford, & Sherman, 1982; Garey & Blakemore, 1977a, b; Garey, Fisken, & Powell, 1973; Garraghty, Salinger, & Hickey, 1984; Guillery, 1972, 1973; Hickey, 1980; Hickey, Spear, & Kratz, 1977; Hubel & Wiesel, 1970; Kalil, 1980; Kratz et al., 1978b; Kupfer & Palmer, 1964; Lin & Sherman, 1978; Movshon & Dursteler, 1977; Sherman et al., 1974; Wan & Cragg, 1976; Wiesel & Hubel, 1963a, 1965a). Other work (Guillery, 1972; Guillery & Stelzner, 1970) has shown that the morphological effect in binocularly lid sutured cats

is equally large throughout the binocular and monocular segments of the LGNd. On the other hand, the morphological effects of monocular lid suture are largely confined to the binocular portion of the LGNd; cell size in the monocular segment of the deprived lamina is more nearly normal.

The geniculate terminations of retinal ganglion cell axons have also been shown to suffer the effects of lid suture by developing abnormally (Garraghty et al., 1986 in press; Sur, Humphrey, & Sherman, 1982). Many X-cell axons arising from the deprived eye have unusually broad, dense terminal fields in laminae A or A1. Y-cell terminations are affected even more dramatically than those of X-cells, but in a different way. Many Y-cell axons from the deprived eye have dramatically shrunken or absent terminal fields in the A laminae.

The main conclusions from these studies in aggregate can be simply stated: The Y-cell system is preferentially influenced by abnormal visual stimulation during the early period of development. More specifically, the Y-cells become less recordable, their average cell body size decreases and their retino-geniculate axonal terminations are severely altered.

Sensitive Period for Visual Deprivation

The concept of a critical period for environmental

influences on visual development was introduced to account for the observation that suturing the lids of one or both eyes in kittens had effects on the Y-cell physiology and average cell body size in the LGNd and the same visual manipulations initiated in adulthood seemed to leave the visual system intact (Wiesel & Hubel, 1963; Sherman & Wilson, 1981). Recent work has concentrated on the details of the time course and limits of this period of susceptibility (Blakemore & Van Sluyters, 1975; Hubel & Wiesel, 1970; Olson & Freeman, 1980; Van Sluyters & Freeman, 1977) as well as the specific effects on individual retinogeniculate axons (Sur & Sherman, 1982) and LGNd cells (Friedlander et al., 1982). In aggregate these deprivation studies support the conclusion that the period in which the Y-cell system is especially responsive to environmental modifications lasts from soon after the time of natural eye opening into the fourth month of life.

The sensitive period defined by these studies appears to coincide with the time course of maximal rate of development of functional and structural properties of LGNd cells during normal development. By the time the cat is 3-4 months of age the physiological properties (Daniels et al., 1978; Mangel, Wilson, & Sherman, 1983; Norman et al., 1977) and cell body sizes of LGNd cells (Hickey, 1980; Kalil, 1978b, 1980) are adultlike. Addi-

tionally, recent work by Sur, Weller, & Sherman (1984) has shown that ganglion cell terminations in the LGNd are not adult-like until the end of the third postnatal month. The critical period also corresponds to the development of spatial acuity in X-cells (Ikeda & Tremain, 1978) and cortical ocular dominance segregation (Hubel, Wiesel & LeVay, 1977; LeVay & Stryker, 1979; Levay, Stryker, & Shatz 1978), leading to the general conclusion that the visual system is structurally and functionally immature at birth and requires a period of time and relatively normal input in order to stabilize into its mature, adult form.

Neurological Effects of Altering the Visual Input of the Mature Organism

The data reviewed briefly above provide strong support for the concept of a critical period for anatomical and physiological development within the visual system. This critical period extends through the third postnatal month and is a time when visual development is particularly susceptible to environmental influence. As described earlier however, the neural substrate for certain visual capacities such as stereopsis must remain relatively more plastic until full physical size of the animal is attained because the geometry and the relationship to the horopter is changing in the growing organism. Evidence for functional plasticity in the mature mammalian

central nervous system in response to alterations in sensory input is accumulating rapidly, and suggests that the conclusions regarding the immutability of the nervous system after the critical period require revision. Salinger and colleagues, for example, have reported a functional response of the LGNd to adult-onset perturbations such as monocular paralysis (Brown & Salinger, 1975; Garraghty, Salinger, MacAvoy, Schroeder, & Guido, 1982; Guido, Salinger, & Schroeder, 1984; MacAvoy & Salinger, 1980; Salinger, 1977; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, Guido, & Schroeder, 1984; Salinger, Schwartz, & Wilkerson, 1977b), binocular paralysis (Salinger, Wilkerson, & MacAvoy, 1977; Wilkerson, Salinger, & MacAvoy, 1977), monocular tenotomy (Salinger, Garraghty, MacAvoy, & Hooker, 1980), and binocular lid suture (Salinger, Schwartz, & Wilkerson, 1977a). Subsequently, Merzenich and colleagues described a functional reorganization of the somatotopic organization of the cutaneous representations of the hand in the cortex of monkeys in which the median nerve was transected (Merzenich, Kaas, Wall, Nelson, Sur, & Felleman, 1983) or digits 1 & 2 were surgically amputated in the adult (Merzenich, Nelson, Stryker, Cynader, Schoppman, & Zook, 1984). Similarly, Eysel and colleagues have also reported functional signs of reorganization in the adult cat lateral geniculate nucleus after removing the output

of one eye by cauterizing the optic disk (Eysel, 1979) or after photocoagulation of large retinal areas (Eysel & Mayer, 1979; Eysel, Gonzalez-Aquilar, & Mayer, 1980). They subsequently determined that the LGNd would respond to less drastic manipulations as well, by placing smaller photocoagulation lesions in the nasal retina of adult cats. Thirty days or more after the lesion, light excitable cells were detected in the originally deafferented LGNd region, with receptive fields in the location of those in the immediate surround of the retinal lesion. All of these experiments have shown that like the developing nervous system, the adult system is capable of responding to modifications in the sensory environment.

The results reported by Salinger and colleagues are perhaps most provocative because their manipulation did not involve complete or even partial sensory deafferentation. Brown and Salingers's (1975) manipulation consisted of transecting cranial motor nerves and did not involve direct damage to the sensory components (Brown & Salinger, 1975; Garraghty et al., 1982; Guido, 1985; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger et al., 1977b; Schroeder, 1985). Nonetheless, Salinger and colleagues have consistently reported the selective functional loss of X-cells in the LGNd following adult-onset perturbations of the visual system and have sought to elucidate and characterize this surprising finding,

focusing on monocular paralysis (Brown & Salinger, 1975; Garraghty, 1984; Garraghty et al., 1982; Guido et al., 1984; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, Garraghty, & Schwartz, 1980; Salinger et al., 1984; Salinger et al., 1977b). After immobilization of one eye for 14 days or more, a significant decrease was found in the proportion of X-cells recorded electrophysiologically in the LGNd (Brown & Salinger, 1975; Garraghty et al., 1982; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger et al., 1977b), and a corresponding increase in Y-cell recordability (Garraghty et al., 1982). Using the same form of eye immobilization, Winterkorn, Shapley, & Kaplan (1981) did not reproduce the X-cell loss. However, their animals were anesthetized during data collection and Garraghty, Salinger, MacAvoy, Schroeder, & Guido (1982) showed that no X-cell loss is found under these conditions.

The morphological effects associated with adult-onset monocular paralysis have also been examined. It has been shown using blind-coded tissue samples that in the LGNd of cats which underwent monocular paralysis as adults, average cell body sizes were smaller than normal (Garraghty, 1984; Garraghty et al., 1982). These soma size reductions were observed throughout only the binocular segment in laminae innervated by the paralyzed eye (Garraghty, 1984). In summary, both the physiological

and morphological results confirm that sensory modifications beginning in adulthood yield visual system modifications well beyond the end of the classically defined critical period for visual system development.

Variability in the Reported Effects of Deprivation

In the previous overview of the effects of infant-onset deprivation, two types of variability were noted: (1) between- subject, and (2) between-experiment. Between subject-variability is reflected by the wide range of values reported for subjects within an experimental condition. For example, deprivation induced changes in cell body size in one study range from 6% to 38% for different 70 day old lid sutured cats (Hickey, 1980). Variability between the results of experiments which are presumably measuring the response to the same stimulus deprivation is shown by between-experiment variability. An example of this is the lid suture induced changes in Y-cell encounter rate which has been reported to range between 45% Y-cells [(essentially no effect)(Shapley & So, 1981)] and 12% (Sherman et al., 1972). This is therefore, a considerable amount of variability, but the source of this variablity is uncertain.

Hypothesis for the origins of variability

The existence of variability of the sort described

above, and of this magnitude, is problematic. While it is possible that measurement error could account for much of the variability, it is important to determine this is so because theories regarding normal visual development and pathology (e.g. Mitchell & Timney, 1984; Sherman & Spear, 1982) depend heavily upon conclusions based on these data. Furthermore, in general, unexplained variability deters the formulation of more accurate theories, and certainly implies that the phenomenon under study is incompletely understood. Data from developmental and adult-onset experiments suggest that the age of the subject at the time of data collection might be of importance in determining the physiological response to deprivation. In general, the Y-cell system is preferentially influenced by abnormal visual stimulation during the early period of development. More specifically, the Y-cells become less recordable (Sherman et al., 1972). After adult-onset deprivation, on the other hand, X-cells in the LGNd are preferentially affected, becoming less recordable (Brown & Salinger, 1975; Garraghty et al., 1982; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger et al., 1977a, b;). This effect has been reported to be consistent both within, and between experiments. It is possible therefore, that if kittens are permitted to mature for longer periods of time with lid suture, some subsequent effect on X-cells might

become evident. If so, some of the variability in the literature, both between-experiment and betweensubject, may be due to a failure to control for the effects of subject age at the time of data collection. It is important to test this hypothesis because it implies that factors other than experience during some early circumscribed sensitive period can operate to control cell body size and X-/Y-cell ratios. This, in turn, has more general implications for the relative malleability of the mature nervous system.

Comparison of the Effects of Infant- and Adult-onset Manipulations

The issue of variability aside, the data reviewed above show that both the infant and the adult nervous systems possess the capacity to respond to sensory perturbations. As in the infant, the adult visual system is quite sensitive to visual insults and will respond dramatically to sensory manipulations. Despite this similarity, however, a major difference exists between the effects of infant and adult-onset perturbations. The Y-cells are the primary targets of early visual deprivation, whereas X-cells are selectively affected following sensory perturbations which begin in the normally-reared adult.

One obvious question which arises after having

reviewed these conclusions is why are the Y-cells affected by early visual deprivation whereas later-beginning insults affect X-cells? Since most of the studies involving a Y-cell loss employed lid suture as a deprivation tool, one might suggest that the sensory deprivations associated with lid suture are specific to the Y-cell system. However, Salinger et al., (1978) found an X-cell loss following two weeks of lid suture in the adult cat. Because lid suture in kittens produces a Y-cell loss, whereas X-cells are affected by the same stimulus disruption in the adult, it seems unlikely that the nature of the deprivation could be the source of the selective effect of infant-onset lid suture on Y-cells. The other obvious possibility is that Y-cells are especially sensitive to anomalous visual input during the critical period as reviewed above, and are relatively insensitive to visual insults after this period. Conversely, X-cells might be especially sensitive to perturbations of the adult visual system, and relatively insensitive to similar insults during kittenhood.

Possible Mechanisms of X- and Y-cell losses.

As was stated previously, Y-cells are immature at birth, relative to the earlier developing X-cells (Daniels et al., 1978; Norman et al., 1977; Sur, Weller, & Sherman, 1984; Walsh et al., 1983), and achieve adult-like physiology and morphology during the third to fourth postnatal

month (Daniels et al., 1978; Norman et al., 1977; Sur, Weller, & Sherman, 1984). There are at least two possible reasons for the apparently selective sensitivity of Y-cells to early visual deprivation. One possibility which has been suggested to account for the selective effect of deprivation on Y-cell development is that the later-developing Y-cells differ fundamentally from the X-cells in that normal visual experience is a necessary condition for the normal development of Y-cells (Sur, Weller, & Sherman, 1984; Sur, Humphrey, & Sherman, 1982). Other aspects of visual system development have been shown to depend upon normal postnatal visual exposure. Examples demonstrating a dependency upon normal visual exposure for normal development include synaptogenesis in visual cortex (Cragg, 1972, 1975; Tieman, Nickla, Gross, Hickey, & Tumosa, 1984) and the development of stereopsis (Barlow & Pettigrew, 1971; Blakemore & Van Sluyters, 1975; Movshon & Dursteler, 1976; Pettigrew, 1974). Alternatively, it is possible that the loss of Y-cells (and presumably the other developmental disruptions) after early visual deprivation does not signal a special sensitivity of these cells to lid suture, but rather that this effect is simply a manifestation of nonspecific vulnerability of Y-cells due merely to the fact that Y-cells happen to be in the midst of a period of rapid development at this early age. In this

view, visual deprivation would be analogous to any of a number of nonspecific teratogenic agents which have effects not because of a special relationship to the affected tissue, but rather because different structures develop at different times, and those undergoing the most rapid growth tend to be most responsive to the introduction of teratogenic agents (Fishbein, 1976). This possibility implies that manipulations which might affect neurological development in general might be shown to selectively affect Y-cell development even under conditions of normal visual exposure, if these manipulations are introduced during the critical period for lid suture effects. This latter possibility seems less likely, however, given the reported differences in the effects of monocular and binocular lid suture (Sherman et al., 1972; Sherman & Spear, 1982). The differences in the effects of monocular and binocular lid suture on the monocular segment suggest that the Y-cell system is responding to the specific environmental influences. In either case, the sensitivity of Y-cells to visual deprivation is clearly confined to the first postnatal months. It has been suggested that during development, X-cells are not sensitive to binocular competitive mechanisms (Sherman, 1979; Sherman & Spear, 1982). This idea came as a result of comparing the effects of lid suture on X- and Y-cells in the monocular

and binocular segments in the deprived laminae. Binocular competitive mechanisms are assumed to be operating in the binocular segment and not in the monocular segment (Guillery, 1972; Sherman, 1979; Sherman & Spear, 1982). After lid suture the X-cells were unable to respond to the highest spatial frequencies throughout both the binocular and the monocular segments. These effects are unlike the Y-cell losses, in which the effects are much more pronounced in the binocular segment. Since X-cells in both segments were affected equally, this result suggests that a binocular competitive mechanism is not involved. On the other hand, a binocular competitive mechanism has been shown to be intimately involved in the effects on X-cells following adult-onset perturbations to the visual system (Garraghty et al., 1982). It seems possible, therefore, that this particular mechanism which affects X-cells in adult-onset deprivations is not activated after the kitten-onset deprivations.

A sensitivity to abnormal patterns of binocular retinal disparity and disruptions in proprioception have been implicated in the loss of X-cells in the mature LGNd after monocular paralysis (Guido, 1985; Salinger, Garraghty, & Schwartz, 1980). Furthermore, normal binocular visual exposure is required for the development of eye alignment (Bennett, Smith, Harwerth, & Crawford, 1980; Blake, Crawford, & Hirsch, 1974; Cynader, 1979; Cynader,

Berman, & Hein, 1976; Sherman, 1972) which is a logical precursor for the postnatal refinement of binocular disparity sensitivity (Blakemore & Van Sluyters, 1975; Pettigrew, 1974). Because, in all of the cases where an X-cell loss has been reported, it has occurred following an adult-onset manipulation in normally reared cats, one wonders why a lid suture beginning in infancy and extending into adulthood wouldn't yield first a Y-cell loss then an X-cell loss. It is possible that X-cells may be spared when early visual deprivations continue into adulthood, not because of a fundamental insensitivity to the manipulations per se, but rather because the mechanism which is responsible for their loss after visual perturbations in normally reared adults is not developed due to the period of deprivation. It seems important to ask, therefore, whether subjects which have been reared with lid suture well into adulthood would also suffer a late X-cell loss which would be superimposed on the Y-cell loss from the infant phase of deprivation since in adulthood binocular competitive mechanisms targeting X-cells would have developed.

Relationship Between the Structural and Functional Consequences of Visual Deprivation

Correspondence. Certain similarities in the patterns of the physiological and morphological effects of monocular

and binocular lid suture suggest that these two effects might be related. That is, after monocular lid suture the physiological loss of Y-cells is much more pronounced in the deprived binocular segment than in the deprived monocular segment (Sherman et al., 1972). Similarly, reductions in average cell body size are much more pronounced in the deprived binocular segment than in the deprived monocular segment with monocular lid suture (Guillery, 1972; Guillery & Stelzner, 1970). After binocular lid suture, there is no difference in the magnitude of the Y-cell loss in the binocular and monocular segments (Sherman et al., 1972). Correspondingly, there is no difference in the magnitude of cell size shrinkage in the binocular and monocular segments (Guillery, 1972; Guillery & Stelzner, 1970). Furthermore, the Y-cell loss in the binocular segment after monocular lid suture is much larger than that seen anywhere in the LGNd after binocular lid suture (Sherman et al., 1972), and there is a correspondingly greater shrinkage of cell size in the deprived binocular segment of the monocular, relative to the binocular, lid suture cats (Guillery, 1972; Guillery & Stelzner, 1970). The existence of these relationships might result in the inference that a causal, or at least a correlational relationship exists between cell size and Y-cell encounter rate such that one could be predicted based on a knowledge of the other.

Lack of correspondence. The generality of the relationship between these measures of LGNd cell physiology and morphology has, more recently, been called to question (Geissert, Spear, Zetlan, & Langsetmo, 1982). Data from deprivation paradigms other than those from deprived laminae in lid suture cats often do not show a correspondence between average cell body size data and X-/Y-cell encounter ratios. For example, Geisert et al. (1982) have shown that when cats have been reared with lid suture and subsequently undergo enucleation of the unsutured eye, cell body sizes return to normal after several months, but Y-cell encounter rate is still reduced. If the lid sutured eye is then opened, the Y-cells can be recorded in normal proportions, but with no additional change in average cell body size (Geissert et al., 1982). Further, in dark reared cats, LGNd cells attain normal size (Kalil, 1978a), but Y-cells are very infrequently recorded physiologically (Kratz et al., 1979). These data show that under certain circumstances, average LGNd cell body sizes and X-/Y-cell ratios can be shown to be dissociable. This raises the question of whether cell body size and X-/Y-cell ratio are each affected by lid suture independently, rather than that changes reported for one of these measures is secondary to those of the other measure, or that the correlation when found

between these measures after simply rearing with lid suture is merely an epiphenomenon of some third variable.

Because both measures have never been reported in the same animal, it is difficult to know whether these two measures really covary even in lid suture. In order to resolve this issue, both anatomical and physiological measures should be taken from the same animals which have been reared with lid suture from early postnatal life.

Summary

Certain salient issues arise from this review of the cat visual system, its development, and its response to perturbations during infancy and maturity. The development of visual perception progresses rapidly in the postnatal kitten with visual acuity and stereopsis reaching adult levels by four months of age. The morphological and physiological features of LGNd neurons are also developed by the end of the fourth postnatal month. One distinct class of visual neurons, namely the Y-cells, is, however, dramatically affected by perturbations such as visual deprivation during early development. This selective effect has been demonstrated both electrophysiologically and anatomically, although a considerable amount of unexplained variability characterizes these observations. These data contributed to the formulation

of the hypothesis for a "critical period" for visual system development, and led to the proposition that the physiological and morphological effects of lid suture were related in some way.

Another line of research has raised questions about earlier aspects of the critical period concept. Under a variety of conditions, the normally developed, mature nervous system has been shown to be physiologically and morphologically responsive to perturbation. With respect to the cat visual system, Salinger and colleagues have shown that adult-onset manipulations reduce recordabililty of X-cells, and not Y-cells. These observations clearly demonstrated that Y-cells were not preferentially responsive to perturbations. Rather, there appeared to be a cell class by age interaction, i.e., Y-cells are disrupted early in development and X-cells are disrupted in the mature animal.

Purpose of the present study

Three questions were raised in this review. (1) When extended well into adulthood, would infant-onset lid-suture, which primarily affects Y-cells, subsequently have an effect on the X-cell system? Alternatively, would the X-cells be protected in a cat whose visual system had suffered the effects of kitten-onset lid suture? (2) Is the age of the subject at the time of

data collection responsible wholly or in part for the unexplained variability in the morphological and physiological effects of lid suture reported in the literature? (3) Finally, are the physiological and morphological effects of lid suture in the LGNd correlated in individual subjects, and does the age of the animal at the time of data collection have any bearing on this relationship? These three questions have been addressed systematically in the present study by examining both the average cell body sizes and encounter ratios for X- and Y-cells in cats reared to varying ages with infant-onset lid suture.

The first question asks if the X-cell effects normally associated with adult-onset deprivations would occur in animals previously deprived with lid suture from infancy? This question addresses the extent to which infant-onset and adult-onset effects on the visual system are interdependent. In other words, is the mechanism responsible for the adult-onset X-cell loss impaired by rearing a cat in a deprived visual environment? This question indirectly addresses the possible mechanism underlying the effects of the two phases of deprivation on both types of cells. For example, if normal visual development is necessary for the adult visual system to respond to adult-onset sensory deprivations morphologically or physiologically, cats whose visual deprivation begins in infancy and which are visually deprived for

extended periods into adulthood should not differ from those deprived for shorter periods of time. That is, once the initial Y-cell system effects occur, the cell body sizes and proportions of X- and Y-cells of visually deprived cats should not change no matter how protracted the deprivation. Alternatively, if aspects of the visual system that are disrupted by infant-onset deprivations (e.g., Y-cells, binocularity) are not involved in the effects on the X-cell system following adult-onset stimulus modifications, then cats reared for long periods of time with one or both eyes sutured might be found to have alterations in the X-cell system as well as the Y-cell system.

The second question examines the source of the wide variability in reports of average cell body sizes and encounter ratios for X- and Y-cells in the LGNd of cats reared with lid suture. This question is addressed by reporting both of these measures for each individual cat. Individual subject data have not previously been reported for the physiological effects and have only occasionally been reported for the morphological effects for animals reared with lid suture. Thus, while a wide range of effects have been reported, it is difficult to determine if the variability in the literature is due to a wide range of individual responses within a group of subjects or if the deprivation effect is in

fact consistent between sujects within a group. As has been suggested in the preceding overview, age of the subject at the time of data collection could be a contributing factor. That is, experiments in which data from older animals were pooled with data from younger animals may have accidently obscured an important age variable and misrepresented the effects of deprivation. Therefore, in addition to reporting both morphological and physiological data for individual cats, age of the subject was investigated as a contributing factor to the degree of lid suture effect.

The third question, which asks the extent to which morphological and physiological effects as measured in previous experiments (average cell body size and X-/Y-cell ratio in the LGNd) are correlated for individual subjects, and how subject age might affect this correlation, has been answered by collecting both sets of data from a subset of the experimental animals. The answers to these three questions contribute not only to an understanding of the underlying mechanisms responsible for the morphological and physiological effects of lid suture, but in a broader sense suggest which epigenetic factors modulate the phenotypic expression of the visual system.

CHAPTER II

METHODS

This experiment addresses three main questions. (1) If a cat is reared from 3-4 weeks postnatal age well into adulthood with lid suture, will additional effects occur in the LGNd which are normally associated with adult-onset deprivations; in other words will the previous lid suture protect the LGNd of older subjects from further changes? (2) Is age of the lid sutured subject at the time of data collection an important factor contributing to the variability of effects of lid suture reported in the literature? (3) To what extent are the morphological and physiological effects of kitten-onset lid suture correlated in subjects of all ages? These questions have been addressed by measuring cell body sizes and collecting X-/Y-cell ratios of LGNd cells in cats reared with lid suture for from several months to several years.

Independent and dependent variables

The independent variable is postnatal age of the subject at the time of data collection. While all subjects underwent lid suture at between 21 and 28 days postnatally,

the subjects vary on the basis of their postnatal age when data are collected. Due to the nature of this experiment, the effects of age of the subject at the time of data collection are inextricably linked to duration of deprivation. These two factors cannot be unconfounded by such maneuvers as delaying the onset of the lid suture, due to the temporal constraints of the critical period. However, for some issues, the nondeprived layers of some subjects serve as age-matched controls for maturational processes.

Two dependent variables were measured in each of the experimental subjects. Electrophysiological encounter ratios for X- and Y-cells were collected only from the hemisphere contralateral to the paralyzed eye. This constraint is imposed by the need to insure accurate receptive field localization of cells and only in the contralateral LGNd are the A and C laminae innervated by the paralyzed eye (see Method, p. 56). Thus due to technical considerations imposed, no electrophysiological data were collected from the hemisphere ipsilateral to the paralyzed eye (only lamina A1 would be from the immobilized eye and therefore receptive field placement and analysis in laminae A and C was not possible). However, this restriction does not apply to the collection of cell body size data. Therefore, in order to increase the sample of cell size data and allow for additional

comparisons between laminae within the same subject, LGNd cell body sizes were measured in the A and A1 laminae in both hemispheres from the same animals which provided the electrophysiological data.

Subjects

In order to be sure of the exact date of birth, all kittens were bred in the laboratory facility. All subjects underwent lid suture at between 21 and 28 days postnatal age. At this age the animals were more likely to survive the lid suture and yet were well within the critical period for visual development (Wiesel & Hubel, 1963a; Sherman & Spear, 1982; Sherman & Wilson, 1981). Data were collected from cats whose ages ranged from 5 months postnatal age (well past the "critical period" for visual development) to over two years of age (well into adulthood). Kittens were assigned to one of seven bins representing age of the subject (and duration of lid suture) at the time of data collection. Each bin represents a four month age interval and two to five animals were assigned to each bin. However, representation was biased toward the younger bins because part of the focus of this study is on the lid suture effect as known in younger animals and the reliability of this effect. Assignment of littermates to the various age bins was spread out across the bins as much as possible so that

within a litter, some kittens were in younger age bins, and others were placed in older age bins. This process could not be completely random since attrition rate claimed a higher proportion of the subjects intended for the older age bins. In order to compensate for attrition, forty one subjects were prepared with lid suture for this experiment. This resulted in twenty-two subjects distributed across the appropriate age bins. An additional three adult cats obtained from the local animal shelter served as controls for hypertrophy of non-deprived cells and as a means of calibrating the present data to the published literature.

Control issues and interpretive problems

Physiological and average cell body size data were collected in normal control animals (acute monocular paralysis: ACMP). These data were compared to those in the existing literature to validate the present procedures of data collection. All subjects underwent monocular paralysis at the start of the first day of physiological data collection (ACMP). This procedure was necessary to allow for subsequent receptive field location and analysis of cells in the LGNd. Results obtained using this method do not differ from other reports in the literature which have used systemic paralytic agents and nitrous oxide for anesthesia. However, for the

present purposes it was necessary to monitor sedation since it has been shown that in adult subjects X- and Y-cell excitability is altered by level of anesthesia (Garraghty et al., 1982; Schroeder, 1984). Since behavioral cues are necessary to monitor level of anesthesia, and such cues are not available in systemically paralyzed animals, ocular paralysis was the method of choice.

Control for possible maturational factors. The independent variable of age at time of recording was a complex one since it included both maturational factors and duration of lid suture. To control for aspects of maturation, electrophysiological and morphological data from deprived laminae were compared to data from the non-deprived laminae in the same subject. One way to control for duration of lid suture would have been to begin the lid suture at later ages. However, constraints imposed by the early onset and short length of the critical period (just three months of postnatal life), and the fact that data already exist showing differences in the effects of deprivation depending on when it begins within the critical period (Van Sluyters, 1978), demand that the lid suture be imposed both early in life, and within a tightly circumscribed window in time. Thus age of subject at the time of data collection and duration of deprivation could not be separated in these experiments.

Control for possible effects of lid suture in the

nondeprived laminae. Some previous experiments have shown that cells in the non-deprived LGNd lamimae can be affected by unilateral deprivations (Garraghty et al, 1985; Hickey et al, 1977; Kuppermann, 1983). In order to insure that some unexplained changes did not occur in the non-deprived laminae in the present experiment, data from these laminae were compared to that obtained from the normal control animals.

Genetic factors. Possible effects of differences/similarities between litters of kittens were controlled by assigning kittens within a litter to different age groups. This is an important control because it has been shown that patterns of neural connections and function vary in different genetic strains of cats (i.e., Siamese cats; Guillery & Cassagrande, 1977). Therefore, littermates were evenly distributed across the age bins. Additionally in order to avoid the most pronounced anomalies, only kittens born of cats with pigmented retinae and skin were used in these experiments.

Lid Suture

At 21 to 28 days postnatal age, each subject was anesthetized with intramuscular injections of ketamine hydrochloride (40mg/kg) and the lids of either the left or the right eye were sutured shut. Removal of the outer edge containing the hair follicles ensured permanent

lid closure. Care was taken to ensure clear lachrymal drainage from the medial canthus of the eye.

Postoperatively each subject was weighed on a daily basis. Antibiotics were administered twice daily and the lid sutures were checked for pinholes and resutured as necessary. All subjects were given a combination vaccination against rhinotracheitis, calici, and panleukopenia at appropriate intervals.

On the day of recording, the sutured lids of the subjects were parted under anesthesia. The closed lids were lifted away from the eye and incised along the entire suture line taking care not to injure the cornea. This allowed for receptive field localization and analysis at the time of recording.

Eye immobilization

All subjects underwent monocular paralysis (Brown & Salinger, 1975; Garraghty et al., 1982; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger et al., 1977b) prior to data collection. Immobilization of at least one eye is necessary for accurate receptive field placement with respect to the visuotopic map in the LGNd (Kaas et al., 1972; Sanderson, 1971a). This procedure has been used successfully by Salinger and colleagues (Brown & Salinger, 1975; Garraghty et al., 1982; Guido et al., 1984; MacAvoy & Salinger, 1980;

Salinger, 1977; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, Garraghty, & Schwartz, 1980; Salinger et al., 1984; Salinger et al., 1977a, b; Wilkerson et al., 1977) as a substitute for systemic paralysis, and has the major advantage of permitting constant monitoring of the animals anesthetic state. Monocular paralysis was accomplished by transection of the cranial nerves III, IV and VI. For reasons of standard procedure, the left eye was paralyzed in all cases. Anesthesia was induced with a mixture of acepromazine maleate (2.9 mg/kg) and sodium pentobarbital (15.0 mg/kg). Vital signs were monitored throughout the procedure, and body temperature was regulated with a waterfilled, feedback-controlled heating pad.

With the animal supported in a supine position, the head was placed in a stabilizing device allowing access to the roof of the mouth. Monocular paralysis involves opening the soft palate at a point 1-2mm posterior to the caudal edge of the palatine bone. The sphenoid sinus was entered using dental burrs to remove overlying tissue and bone. The cranial nerves were lifted separately and sectioned as they converged on the orbital fissure. This transbuccal approach has been employed to minimize trauma to the orbit, optic nerve and central structures (Garraghty et al., 1982; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger et al., 1977b). It is important

to note that during the course of this surgery, direct damage to the central nervous system is avoided by leaving the meninges intact. This precaution minimized both the chance that changes secondary to accidental damage would affect the results, and that subjects would be lost prematurely due to infection of the neural tissue. The surgery does not produce accidental damage to orbital contents or cranial nerve II since their bony coverings were left intact. Postoperatively, each animal's weight was checked daily. Twice daily they were given antibiotics and the immobilized eye was examined to see that it remained clear and viable.

Craniotomy and Pedestal

Craniotomies were performed over the right lateral geniculate nucleus (anterior 3.0-8.0; lateral 8.0-12.0) and the right side of the optic chiasm (anterior 14.5; lateral 2.0; Snider and Neimer, 1961). A pedestal of dental acrylic with three bolts embedded was then constructed around three anchoring screws mounted on the animal's skull. The pedestal allowed the head to be securely affixed in the stereotaxic apparatus during recording sessions and thereby obviated the need for painful ear and eye bars. This procedure, patterned after that of Orem, Schlag-Rey and Schlag (1973), permited daily microelectrode recording from an easily tended, sedated

animal. In addition, because the pedestal was securely cemented to the skull and bolted into the stereotaxic apparatus on successive recording days, the use of a pedestal permited more accurate placement of the micro-electrode.

Optic Chiasm Electrode Placement

A bipolar stimulating electrode was then implanted in the right side (which is contralateral to the paralyzed eye) of the optic chiasm. Stainless steel, teflon insulated wire was wound into a bipolar electrode with uninsulated tips of 0.5 mm, and vertical tip separation of 2.5 mm. This electrode was implanted 2 mm to the right of the optic chiasm (lateral 2.0 mm; Snider & Niemer, 1961). The electrode was placed in the rostro-caudal midpoint of the chiasm which was defined by electrophysiological mapping. Salinger and colleagues have found that such a mapping procedure reduces between animal variability in average optic chiasm latency distributions. Following appropriate placement, the electrode was permanently affixed to the skull and pedestal with dental acrylic.

Physiological Data Collection

At the beginning of each daily recording session, animals were sedated with a mixture of acepromazine maleate (2.9 mg/kg) and sodium pentobarbital (15.0 mg/kg)

and bolted into the stereotaxic apparatus. During each recording session, the corneas were protected with plano-contact lenses. The animal's body temperature was regulated and respiration rates were carefully monitored.

Extracellular activity from single units in the lateral geniculate nucleus was recorded using tungsten microelectrodes insulated with Epoxylite, with tip diameters of approximately 1 micron and impedences of 10-20 megohms at 1000 Hz. Postsynaptic action potentials were amplified by a WPI DAM-5 preamplifier and a Grass AC amplifier. This amplified output was displayed on a Tektronix T912 storage oscilloscope and identified according to the criteria of Bishop, Burke, and Davis (1962). The criterion which is usually noted first is the shape of the response, which is very different for an axon and a LGNd cell. The response of an axon is initially of simple monophasic shape, positive-going and of relatively short duration. In amplitude the responses of axons vary considerably, the majority lying between 1 and 10 mv. The response behaves in all-or-nothing fashion when the strength of the stimulus is varied. This contrasts with the LGNd cell which responds as a complex positive-negative waveform. The exact waveform and the ratio of the amplitudes of the positive and negative phases as well as the overall amplitude vary considerably and depend critically on the distance of the tip of the electrode from the unit.

The absolute latency does not provide a certain test for many units because the optic nerve contains fibers with a wide range of conduction velocities. Thus some LGNd cells and radiation axons may have brief latencies while small tract axons may have longer latencies. In post-synaptic units the change of latency is particularly marked with stimuli near threshold and if the stimulus is set at threshold, the play of latency to successive stimuli may be quite large. On the other hand, a presynaptic unit shows very little play of latency at threshold. It is known from previous work that optic nerve fibers will respond to tetanic stimulation at rates of up to 1000 Hz, at least for short periods of time. LGNd cells on the other hand, fail to respond after only three or four stimuli at rates of a few hundred Hz.

The optic disk of the immobilized eye was plotted on a tangent screen one meter from the disk using the method of Fernald and Chase (1971). Receptive fields of lateral geniculate cells driven by the immobilized eye were located on the screen, with their positions relative to optic disk recorded. Receptive field positions of cells in lamina A1 were estimated from fields of cells recorded in the layers above and below this layer (laminae A & C cells) which are driven by the paralyzed eye, since it is known that the visual maps of these laminae are in register (Bishop et al., 1962; Kaas et

al., 1972; Sanderson, 1971a).

Electrical stimulation of the optic chiasm (OX) consisted of 1-15V square wave pulses delivered through a stimulus isolation unit. The latency of the displayed action potential represented the time interval separating the optic chiasm shock from the weighted average of the latency onset of the geniculate action potential (i.e., the foot of the action potential).

Sedation

Initial reports on the effects of monocular paralysis (Brown & Salinger, 1975; Salinger et al., 1977b; Salinger, Garraghty, MacAvoy, & Hooker, 1980) involved data from subjects which were sedated with initial intraperitoneal injections of acepromazine maleate (2.9 mg/kg) and sodium pentobarbital (5.0 mg/kg). Since these earlier studies, it has become clear that a concentration of sodium pentobarbital sufficient to produce anesthesia can actually suppress the effects of monocular paralysis (Garraghty et al., 1982; Winterkorn, Shapley, & Kaplan, 1981). Unfortunately no data are available on the importance of level of anesthesia on the kitten-onset lid-suture preparations which are routinely anesthetized during recording. In order to permit comparison with other data recorded in this lab, however, cellular recordings were obtained from animals which are sedated and not

anesthetized.

Sedation was behaviorally defined as acceptance of painless head restraint (i.e., using the skull-mounted acrylic pedestal rather than eye and ear bars), but with retained responsiveness to noxious stimuli, capability of ataxic locomotion upon release from head restraint, visual tracking with the mobile eye during recording, maintenance of normal respiratory and temperature values, and ability to feed following daily recording sessions. Maintaining this level of sedation required supplemental doses of sodium pentobarbital at a rate of 2.6 mg/kg/hr, on the average (Garraghty et al., 1982).

Cell Classification

OX latency and four receptive field response measures (center size, response to moving gratings, degree of centersurround antagonism, and response to rapidly moving centerinhibiting stimuli) were taken, with receptive field data taken prior to OX latency. Classification criteria were identical to those reported previously (Garraghty et al., 1982; Guido, 1985; Guido et al., 1984; Salinger et al., 1984; Schroeder, 1985) and cells were classified as X or Y unless more than one of the tests was in disagreement.

Morphological data collection

On the final day of electrophysiological data collection, each subject was deeply anesthetized with sodium pentobarbital (55 mg/kg) and perfused through the heart with 500 ml of physiological saline (0.9%) followed by 500 ml of 10% formalin in saline. Each brain was then removed from the skull, blind-coded, and stored in a solution of 30% sucrose in 10% formalin. Complete infiltration of the brain by 30% sucrose greatly facilitated sectioning with the freezing microtome. Following infiltration, signalled by the brain sinking in the fixative, which takes about 3 days, unnecessary areas of the brain surrounding the lateral geniculate nucleus were cut away. Blocking out a portion of the brain which contained the LGNd, besides reducing the total amount of brain to be cut, provided a flat surface for horizontal placement onto the freezing stage as well as a flat surface to begin cutting. In order to anchor the brain to the freezing stage, a platform was formed by freezing successive layers of the sucrose/formalin mixture in which the brain had been stored. The brain was then thoroughly attached to this platform, again using the sucrose/formalin mixture. Before the brain was completely frozen by surrounding it with finely granulated dry ice, an artifact (in this case a hole in the white matter) was placed in the right hemisphere as an aid in future distinctions between right and left hemispheres. After the brain

was frozen, 70u sections were cut in the coronal plane, caudal to rostral through the LGNd. Sections were collected in small compartments filled with 10% formalin and allowed to incubate for 2 to 3 days before mounting out of phosphate buffer (pH 7.4) onto chrom-alum treated glass slides. The mounted sections were allowed at least one day to dry thoroughly and then were stained with cresyl violet acetate using the Nissl method (Appendix 1).

Only those sections at the coronal plane representing the anterior-posterior midpoint of the LGNd were used for sampling. The identification of this coronal level is reliable since it requires simply sampling the section which lies midway between the anterior-most and posterior-most sections containing portions of the LGNd. Soma size measurements of 100 cells were obtained from the medial third (which represents the medial 5o of visual space) of each deprived and non-deprived layer A and A1 of both hemispheres (400 cell body measurements per subject). An outline of a section at the rostro-caudal midpoint of the LNGd was shown in Figure 2. This section was labeled to indicate the various eccentricities. Sampling only those cell bodies in the medial one third at coronal 5 (Sanderson, 1971a, b) of the geniculate body ensures both that only those cells which also were sampled electrophysiologically were included in the morphological sample and that similar groups of cells

were sampled from each cat. Sampling began randomly at either the dorsal or ventral edge of the geniculate lamina and successive sweeps continued laterally until 100 cells were measured.

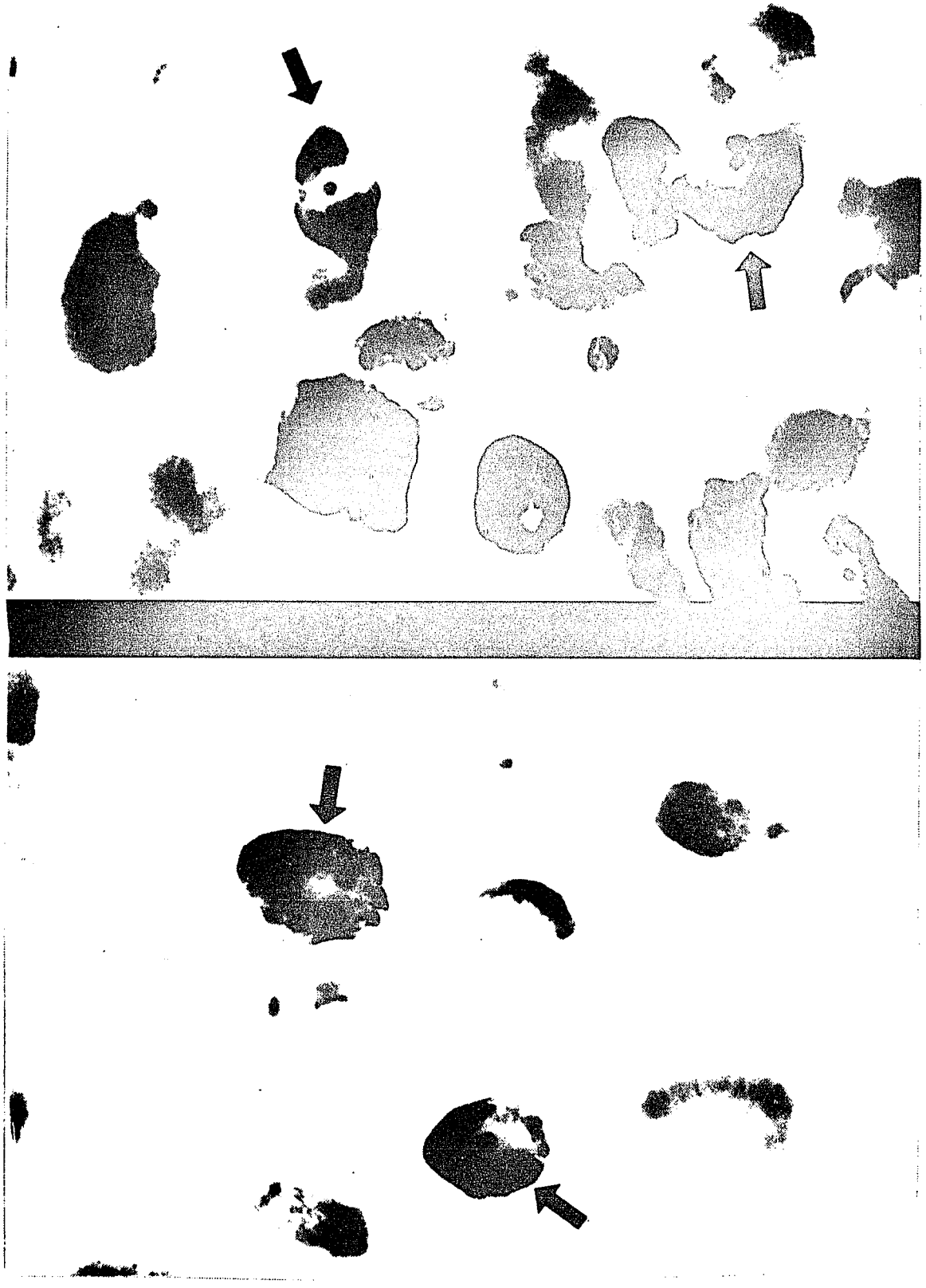
Only those cells judged to be neurons on the basis of a clear nucleolus and Nissl substance (Garraghty & Salinger, 1984; Garraghty et al., 1984; Garraghty, Salinger, & MacAvoy, 1985; Hickey, 1980; Hickey et al., 1977; Kalil, 1978a, b; Kalil, 1980; Murakami & Wilson, 1983) were sampled. Figure 3 illustrates several neuronal cell bodies and demonstrates that cell outlines can unambiguously be determined. Sections were viewed at 1000X using an Olympus Vanox microscope. Cell outlines were then drawn with the aid of a drawing tube. These cell outlines were then quantified and stored by using the Bioquant II (R & M Electronics) software. In order to accomplish this, outlines of cell bodies in the blind-coded tissue were traced with a special pen over a digitized drawing pad which transfered this information into the computer. Each cell outline was reproduced on a cathode ray tube screen along with the quantified cell body size and number.

Statistics

These experiments involved the collection of both morphological and physiological data in visually deprived

Figure 3. Photomicrographs of LGNd individual cell bodies stained for Nissl substance with creysl violet acetate. As the focal plane is moved throughout the thickness of the section, a clearly defined nucleolus within the nucleus can be seen. At this point the cell outline can be drawn.

Figure 3



and normal cats. Included in the data analysis were electrophysiological data previously obtained from kitten onset bilaterally lid sutured cats (Salinger et al., 1978). Additionally when possible, cell body sizes were measured in these subjects and included in the analyses. The questions addressed here required the use of a variety of statistical techniques.

The preliminary results suggested that subjects can be divided into at least two groups on the basis of age of the subject at the time of data collection. Since the oldest subject in which a Y-cell loss was observed was sixteen months old, for purposes of group comparisons, this age was the cut off for animals in the "young" condition. Subjects 17 months or older fell into the "older" condition. Data obtained from deprived laminae in younger cats and from the deprived laminae in older cats were compared with those from normal controls (ACMP). Statistical comparisons were also made between data from the young deprived laminae and those from the deprived laminae of older cats. Additionally, young and old deprived laminae data were compared to data from the young and old non-deprived laminae, respectively. For both the physiological and morphological data, the MannWhitney test (Daniel, 1978) was used. These comparisons provided the answer to the first question regarding whether or not a previous

lid suture would protect the LGNd of older subjects from further adult-like effects of lid suture. Second, as was evident in the preliminary observations, there was reason to believe that a trend existed in both the electrophysiological and morphological data such that age-dependent changes would be found in these data. For this reason, both morphological and physiological data from the deprived laminae and those from the non-deprived laminae from individual cats were submitted to the Cox-Stuart test for trend analysis (Daniel, 1978). This statistic would reveal the trend for X/Y ratio or cell body size to change with age of the subject at the time of data collection.

Finally, comparisons were made between the morphological and physiological data from the deprived laminae of individual cats in which both measures were taken. To accomplish this, a Spearman rank correlation coefficient (Daniel, 1978) was used to determine the degree to which cell body size and X/Y ratios in the LGNd are correlated.

CHAPTER III

RESULTS

Twenty-two kittens were reared with lid suture which began at 3-4 weeks and continued for varying lengths of time. The postnatal ages of the subjects at the time of data collection ranged from 5 to 30 months. Thus, lid suture duration, which covaries with age at the time of data collection, ranged from 4 to 29.25 months. X-/Y-cell encounter ratios and/or cell body sizes were taken from both the deprived and nondeprived laminae of each subject. In order to be consistent with the literature, these LGNd cell encounter ratios are reported as percentage of Y-cells. Because the percentage of intermediate or mixed cell types is small (4-5%, see Garraghty, 1985 for review), for any change reported in the Y-cell population there is a complementary change in the X-cell population. Also to be consistent with the literature, neuronal sizes are reported as average cell body size.

The physiological data (i.e.,Y-cell percentages) are based on a total of 1,662 cells recorded in the deprived and nondeprived laminae of 22 cats. Recordings were confined to areas of the LGNd representing the

central 5 degrees of visual space. The physiological data representing normal controls were taken from previously reported acute monocular paralysis (ACMP) subjects (Garraghty et al., 1982; Salinger et al., 1977a, b; Salinger, Garraghty, MacAvoy & Hooker, 1980; Salinger, Garraghty & Schwartz, 1980). The Y-cell percentages taken from these subjects do not differ significantly from other reports on normally reared cats (Garraghty et al., 1986; Hoffmann et al., 1972), and thus constitute adequate controls.

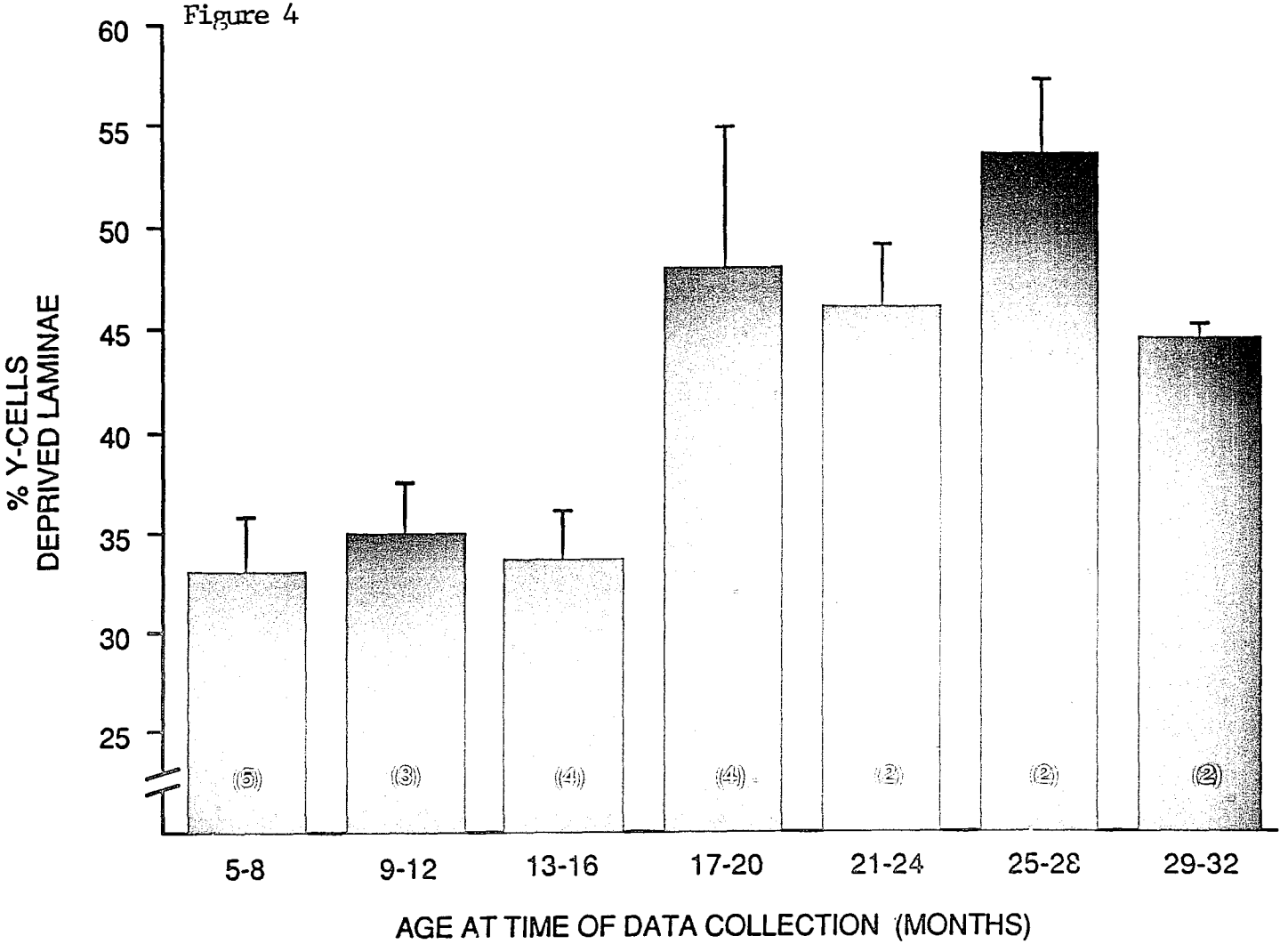
Four hundred cell body size measures were taken from corresponding areas of the LGNd in both hemispheres of each of 19 visually deprived cats for a total of 7,600 measured cells. Three of the normal control subjects from which physiological data were taken also supplied the morphological data for the normal control. As with the experimental subjects, four hundred cell body size measures were taken from each subject for a total of 1,200 cell body measurements from normal subjects. Thus, the total number of soma size measurements taken was 8,800.

Physiology

Deprived laminae. Figure 4 displays the percentage of Y-cells recorded in the deprived laminae of the experimental cats. Values on the ordinate designate percentage of Y-cells. The age of the subject at the time of data

Figure 4. Histogram of percentage of LGNd Y-cells in laminae innervated by the deprived eye from subjects which were reared with infant-onset lid suture to various postnatal ages. Subjects are grouped into age bins of 4 month intervals. The vertical bars represent the standard deviation for the means of all subjects within an age group. The number of subjects within each group is indicated in parentheses.

Figure 4

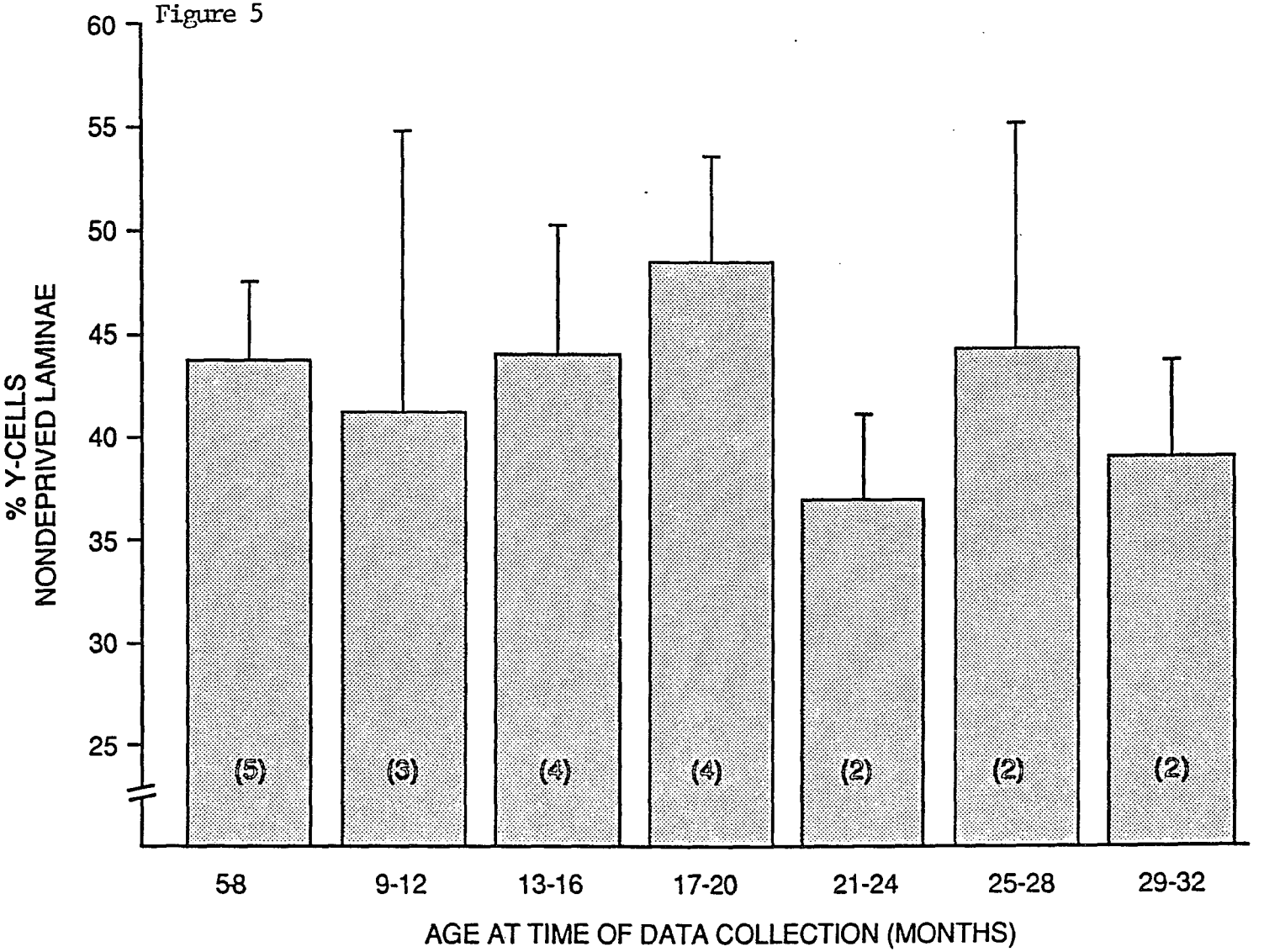

60
55
50
45
40
35
30
25
% Y-CELLS
DEPRIVED LAMINAE
(5)
(3)
(4)
(4)
(2)
(2)
(2)
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

collection is represented on the abscissa. For display, subjects were grouped into age intervals of 4 months duration, starting at 5 months postnatal and extending to 32 months. The average percentage of Y-cells encountered in the deprived laminae is 40.2%. This is not significantly different from the value obtained from normal controls (41%, Mann-Whitney, $p > .05$). However, an abrupt shift is clearly evident at 17 months and thus the effects of lid suture vary widely among the subjects. There appears to be a tendency for the cats with short periods of lid suture to be deficient in Y-cells and for the cats with longer periods of lid suture to show less of a deprivation effect, or more Y-cells. However, statistically, it is necessary to report the data from the nondeprived laminae, because these are the appropriate laminae for comparisons for the deprived laminae.

Nondeprived laminae. Figure 5 illustrates the percentage of Y-cells encountered electrophysiologically in the laminae innervated by the open eye of cats reared with lid suture. The average percentage of Y-cells encountered in the nondeprived laminae of the experimental subjects is 43.4%. This value can be compared to 41% encountered in the normal control subjects. As would be expected from these nearly identical averages, a Mann-Whitney comparison based on the percentage of Y-cells in the nondeprived laminae showed no significant difference

Figure 5. Histogram of percentage of LGNd Y-cells in laminae innervated by the nondeprived eye from subjects which were reared for varying durations with infant-onset lid suture. Subjects are grouped into age bins of 4 month intervals. Symbols as in Figure 4.

Figure 5


60
55
50
45
40
35
30
25
% Y-CELLS
NONDEPRIVED LAMINAE
(5)
(3)
(4)
(4)
(2)
(2)
(2)
58
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

between the lid sutured and normal control animals (M-W, $p > .10$).

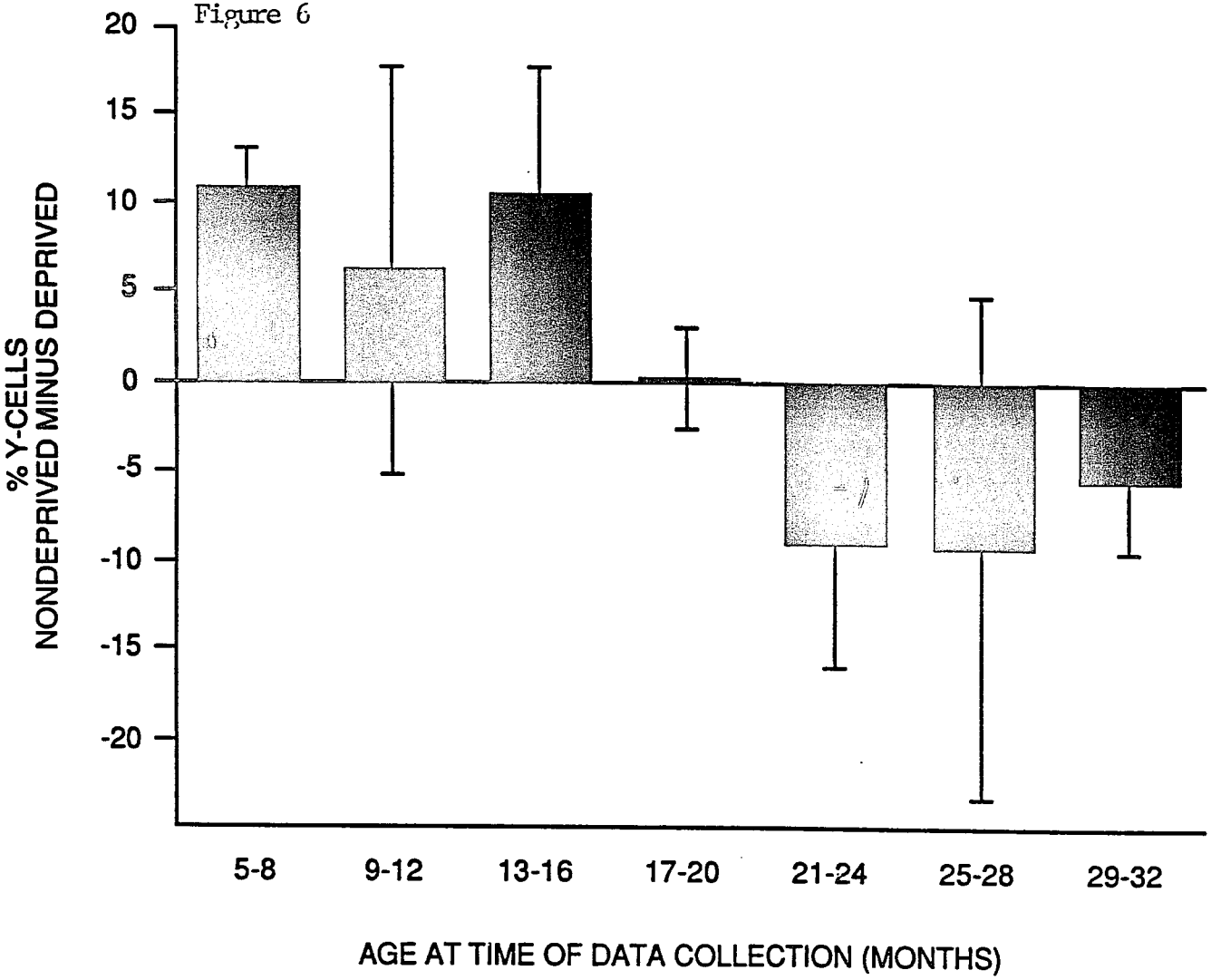
Effects of lid suture over time using the nondeprived laminae for comparisons. Using the nondeprived layers as a control to examine the effects of deprivation on deprived layers allows using comparisons with each animal as its own control. This permits one to control for possible betweensubject differences in absolute Y-cell encounter rate values arising from individual differences or such factors as the precise eccentricities sampled. These differences in the percentage of Y-cells encountered are illustrated graphically in Figure 6. One can readily detect in contrast to the younger subjects, a trend for the older subjects to show the same number, if not more, Y-cells in the deprived relative to the nondeprived laminae. The mean differences between the deprived and the nondeprived laminae for the three groups of younger subjects in order of increasing age were 10.8%, 6.3% and 10.6%. The mean differences for the older subjects also in order of increasing age were .4%, -8.9%, -9.2%, and -5.5%. A Cox-Stuart test for trend on these differences showed that although the initial effect of deprivation is to reduce the percentage of Y-cells, with increasing age of the subject past 17 months, the percentage of Y-cells increases (Cox-Stuart, $p < .01$).

The basis for this significant trend is evident

Figure 6. Histogram showing the percentage of Y-cells for each age bin when the percentage of Y-cells in the deprived laminae are subtracted from the percentage in the nondeprived laminae. The zero horizontal line indicates no difference between deprived laminae Y-cell percentages and nondeprived laminae Y-cell percentages. Values above the line indicate that there were fewer Y-cells in the deprived than in the nondeprived laminae and values below the zero line would indicate that there were more Y-cells in the deprived laminae than in the nondeprived laminae.

Symbols as in Figure 4.

Figure 6


20
15
10
5
0
-5
-10
-15
-20
% Y-CELLS
NONDEPRIVED MINUS DEPRIVED
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

from a visual inspection of the present physiological data. It seems clear that the experimental animals can be divided into two groups on the basis of subject age at the time of data collection. For every group of subjects 16 months or younger, the percentage of Y-cells in the deprived laminae falls far below that in the nondeprived laminae. Conversely, for every group of subjects 17 months of age and greater, the percentage of Y-cells in the deprived laminae equals or exceeds that in the nondeprived laminae of the same cats. Furthermore, in these older subjects, the percentage of Y-cells in the deprived laminae also equals or exceeds normal values. Mann-Whitney comparisons on these two groups (young and old) using the difference between the nondeprived and deprived laminae in each show that they are statistically different from one another ($p < .01$). Thus age of the subject at the time of data collection and its covariate, duration of deprivation, are important variables in determining whether a deprivation effect will be seen following infant-onset lid suture. In animals where postnatal age at the time of data collection was 16 months or less, visual deprivation had a pronounced effect, in that proportions of Y-cells in deprived laminae of the LGNd were less than in nondeprived laminae. This deprivation effect seems to disappear abruptly upon reaching 17 months of age or older and another

effect is evident. That is, as duration of lid suture increases past 17 months postnatal age, the percentage of recordable Y-cells increases.

Because the difference in percentage of Y-cells between the deprived and nondeprived laminae appears to change direction after 16 months and the percentage of Y-cells in the nondeprived laminae does not change as a function of age, it seems likely that the changes in the percentage of Y-cells must be occuring in the deprived laminae alone. Figure 7 graphically explores this inference by plotting the percentage of Y-cells in both the deprived and nondeprived laminae for each groupof cats across all ages studied. It is clear from the graph that in the nondeprived laminae, the percentage of Y-cells does not change with age and duration of lid suture. On the other hand, with increasing subject age and duration of lid suture, the effects of lid suture in the deprived laminae are drastically reduced. These observations are substantiated statistically (nondeprived, young vs old, $p > .10$, deprived, young vs old, $p < .01$).

Morphology

Deprived laminae. Figure 8 is designed to show qualitatively the morphological effects of lid suture on the LGNd with a normal LGNd included for comparison. Part (a) is a photomicrograph of a normal Nissl stained

Figure 7. Histogram of percentage of LGNd Y-cells in laminae innervated by the deprived eye (solid bars) and by the nondeprived eye (stipled bars) following infant-onset lid suture which was allowed to persist for varying lengths of time. Subjects are grouped into age bins of 4 month intervals. Symbols as in Figure 4.

Figure 7

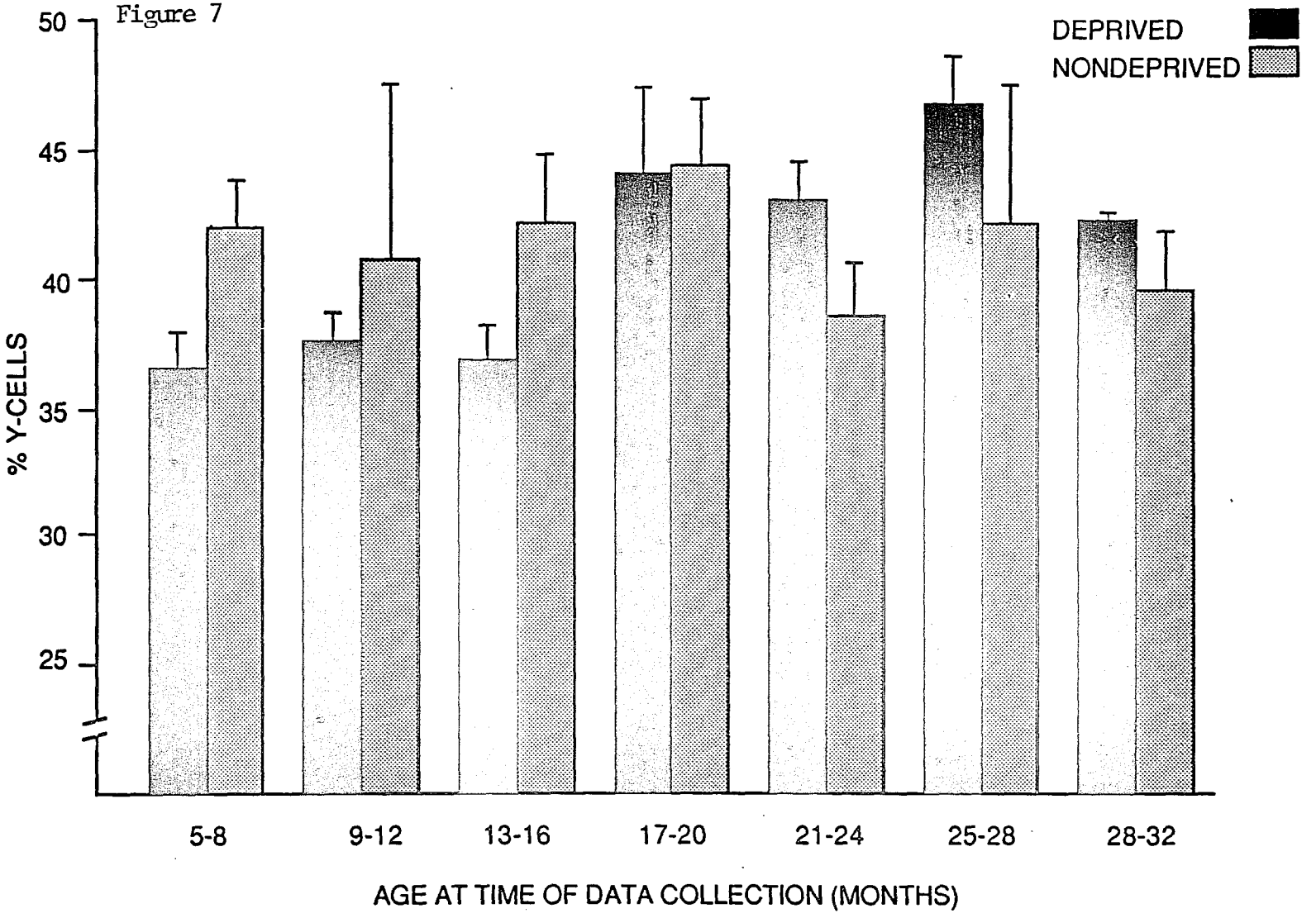
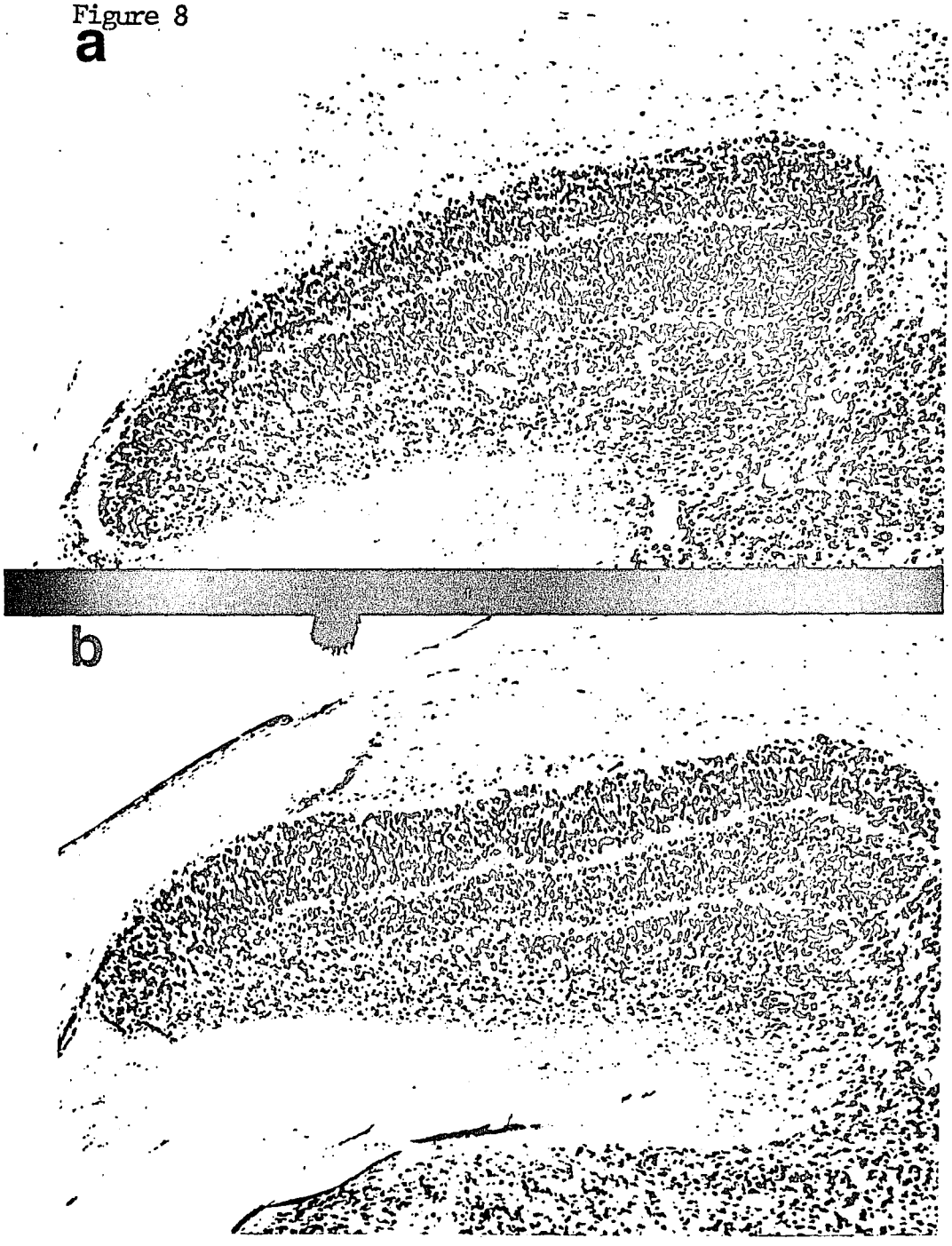

DEPRIVED
NONDEPRIVED
50
45
40
35
30
25
% Y-CELLS
5-8
9-12
13-16
17-20
21-24
25-28
28-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

Figure 8. a. A photomicrograph of a normal Nissl stained LGNd from the left hemisphere. Both laminae A and A1 are about equal in size and have accepted comparable levels of stain.

b. A photomicrograph of a Nissl stained left LGNd from a lid sutured cat in which data were collected at 6 months postnatal age. In this experimental subject it is quite obvious that lamina A1 is innervated by the deprived eye. It appears lighter than the normally innervated lamina A, probably because the shrunken cell bodies have less Nissl substance and therefore accept less cresyl violet acetate.

Figure 8



LGNd from the left hemisphere. Both laminae A and A1 are about equal in size and have accepted comparable levels of stain. Part (b) is a photomicrograph of a Nissl stained left LGNd from a lid sutured cat in which data were collected a 6 months postnatal age. In this experimental subject, it is quite obvious that lamina A1 is innervated by the deprived eye. It appears lighter than the normally innervated lamina A, probably because the shrunken cell bodies have less Nissl substance and therefore accept less cresyl violet acetate. Since hypertrophy of cells, or an increase in the average cell body size above normal, has been reported (Hickey et al., 1977; Kuppermann, 1983), although not consistently (Kalil, 1980), neuronal size data from the deprived laminae must be compared to those from normal controls to eliminate the contamination by possible hypertrophy of cells in the nondeprived laminae. Figure 9 illustrates average cell body size data taken from cells in the deprived laminae of all subjects. The mean cell body size for the deprived laminae is 200.2um2. This can be compared to 251um2 in the normal controls. This 21.2% reduction in average cell body size is statistically significant (M-W, $p<.01$).

Nondeprived laminae. Figure 10 presents average cell body size data for cells measured in laminae A and A1 innervated by the nondeprived eye. The average

Figure 9. Histogram of average cell body size (um^2) of LGNd cells which receive afferent input from the deprived eye of subjects reared to varying ages with infant-onset lid suture. Subjects are grouped into age bins of 4 month intervals. Symbols as in Figure 4.

Figure 9

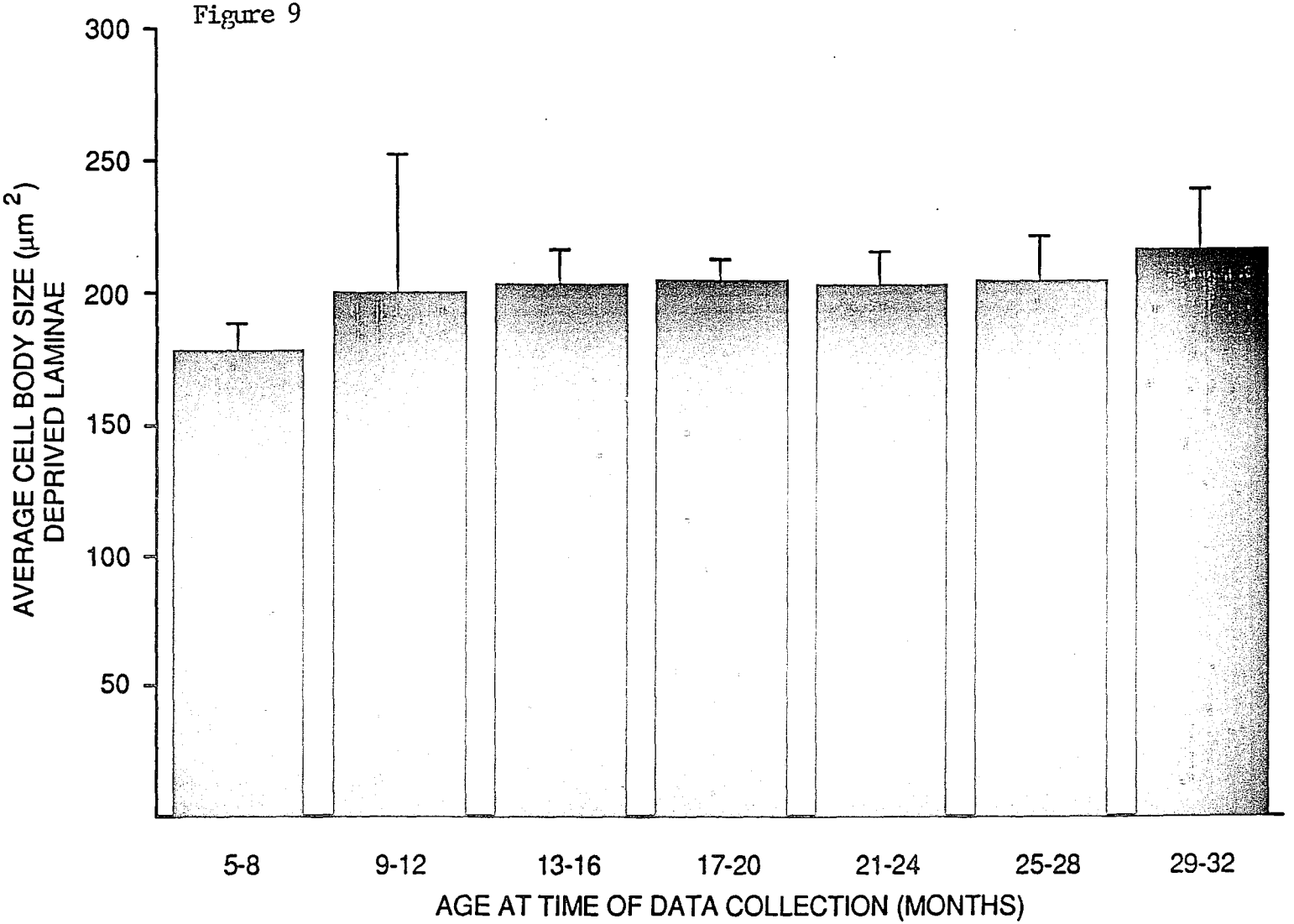
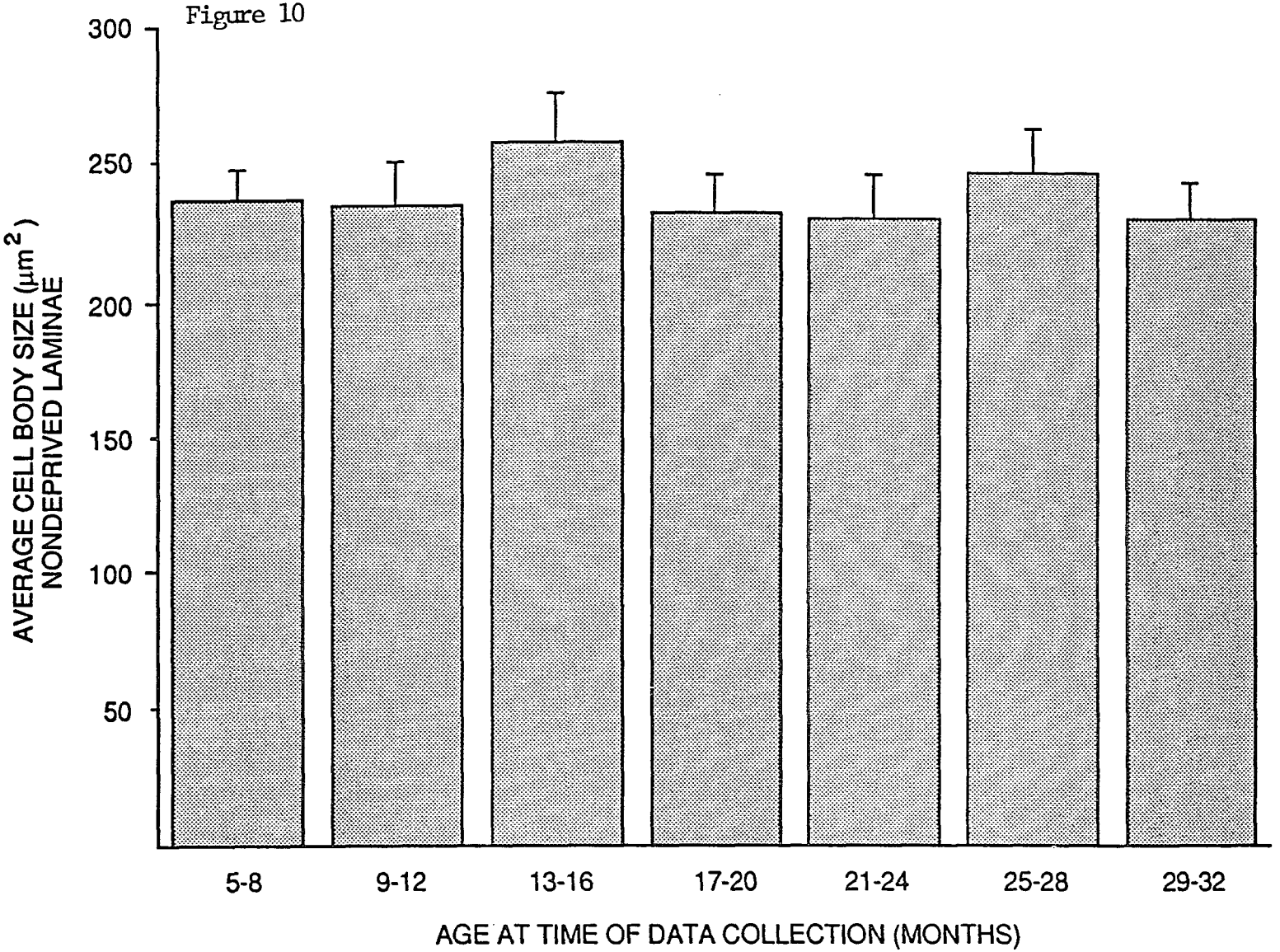

300
250
200
150
100
50
AVERAGE CELL BODY SIZE (μm 2)
DEPRIVED LAMINAE
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

Figure 10. Histogram of average cell body size (um^2) of LGNd cells which receive afferent input from the nondeprived eye of subjects reared to varying ages with infant-onset lid suture. Subjects are grouped into age bins of 4 month intervals. Symbols as in Figure 4.

Figure 10


300
250
200
150
100
50
AVERAGE CELL BODY SIZE (μm²)
NONDEPRIVED LAMINAE
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

cell body size in the nondeprived laminae is 238.8um2. This value does not differ significantly from that obtained from the normal controls (251um2, M-W p >.10). It is also clear from this figure that there are no obvious systematic changes in cell body size with age of the subject.

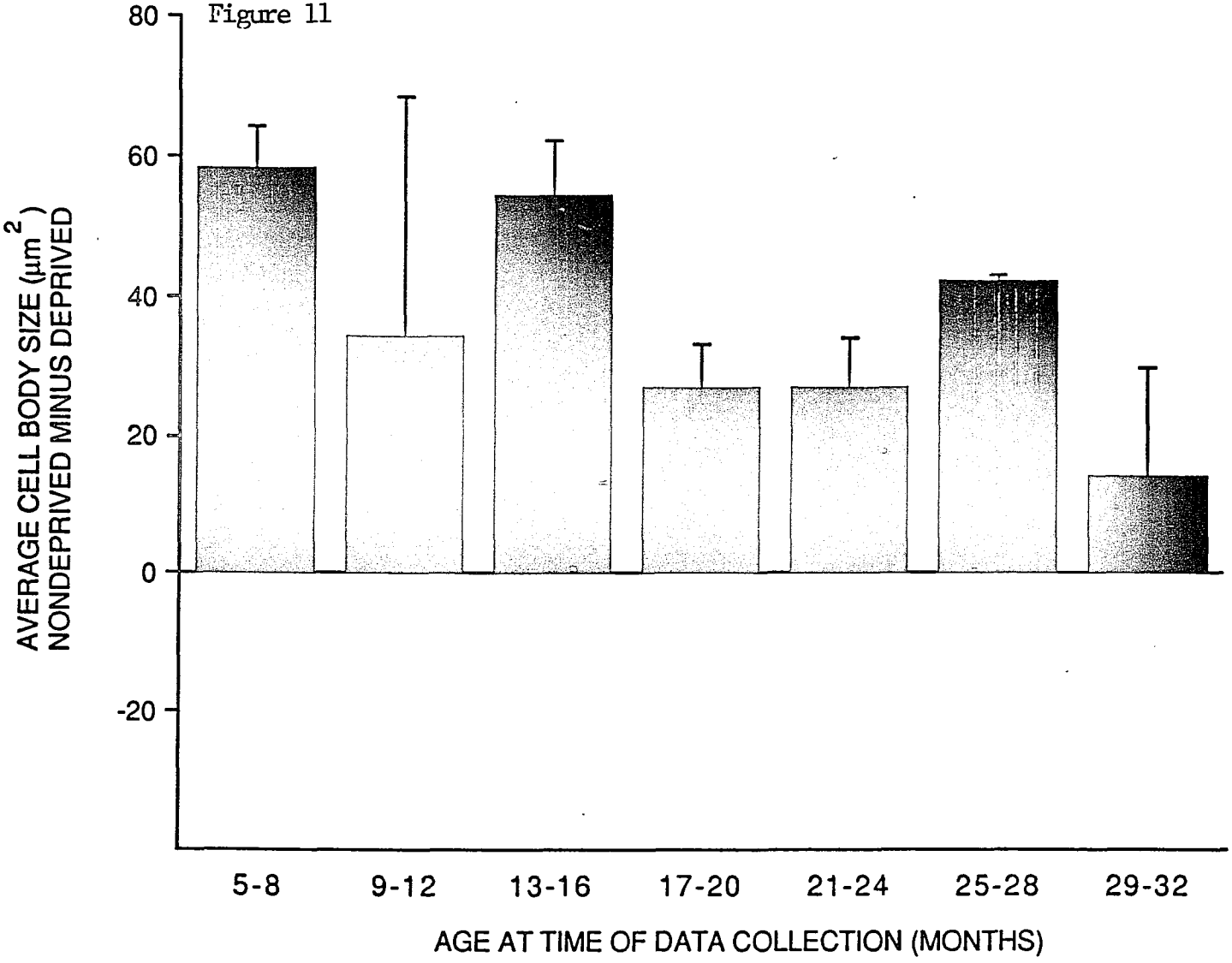
Certainly, there is no evidence for hypertrophy of cells in the nondeprived laminae of these cats. Moreover, the values obtained for the nondeprived laminae in the present experiments are in good agreement with normal values in the literature (Garraghty et al., 1984; Garraghty, Salinger, & MacAvoy, 1985; Guillery, 1966; Hickey, 1980; Hickey et al., 1977; Kalil, 1978a, b, 1980; Spear & Hickey, 1979), reinforcing the notion that the nondeprived somata in the present study are normal in size. Since it has been shown that the nondeprived laminae have not experienced hypertrophy, the nondeprived data can now be used for within-animal comparisons.

Effects of lid suture over time using the nondeprived laminae for comparisons.

Figure 11 presents the differences between the average soma size in the deprived and nondeprived laminae of the seven age groups of subjects. These differences represent the deprivation effect on morphology. The difference means of each age bin by increasing age are 58.8, 34.2, 53.8, 26.8, 26.7, 45.9, and 13.9um2. The

Figure 11. Histogram showing the average cell body sizes for each age bin when the mean soma sizes in the deprived laminae are subtracted from the mean soma sizes from the nondeprived laminae. The zero horizontal line indicates no difference between deprived laminae soma sizes and nondeprived laminae soma sizes. Values above this line indicate that there were smaller soma sizes in the deprived laminae than in the nondeprived laminae and values below this zero line would indicate that there were larger soma sizes in the deprived laminae than in the nondeprived laminae. Symbols as in Figure 4.

Figure 11


80
60
40
20
0
-20
AVERAGE CELL BODY SIZE (μm^2)
NONDEPRIVED MINUS DEPRIVED
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

relative difference between cell body size in deprived and nondeprived laminae appears to decrease in the older ($\geq$ 17 mo.) animals, relative to the differences for the younger (< 17 mo.) animals. This change over time is statistically significant (M-W, $p < .05$). However a Cox-Stuart test for trend is not statistically significant (C-S, $p = .054$), suggesting that the effect of age is a stepwise trend occuring at about 17 months of age postnatal.

The effect of age is quite obvious qualitatively as can be seen in Figure 12. This is a photomicrograph of the left LGNd of a lid sutured subject which was 29 months old at the time of data collection. It is clear that the large differences in Nissl staining which were seen between the deprived and nondeprived laminae in younger subjects (<17 months, Figure 8), is no longer evident in this older subject.

A reduction in the degree of difference in the sizes of neurons in the deprived and nondeprived laminae represents a deprivation effect and a parallel effect of that found physiologicaly. This reduction could occur for three reasons. First, cell size in the deprived laminae could grow somewhat, becoming more nearly normal in size. Second, cells in the nondeprived laminae could shrink somewhat, becoming more like cells in the deprived

Figure 12. A photomicrograph of the left LGNd of a lid sutured subject which was 29 months old at the time of data collection. It is clear that the large differences in Nissl staining which were seen between the deprived and nondeprived laminae in younger subjects (<17 months) is no longer evident in this older subject.

Figure 12

laminae. Or obviously, both of these things could occur.

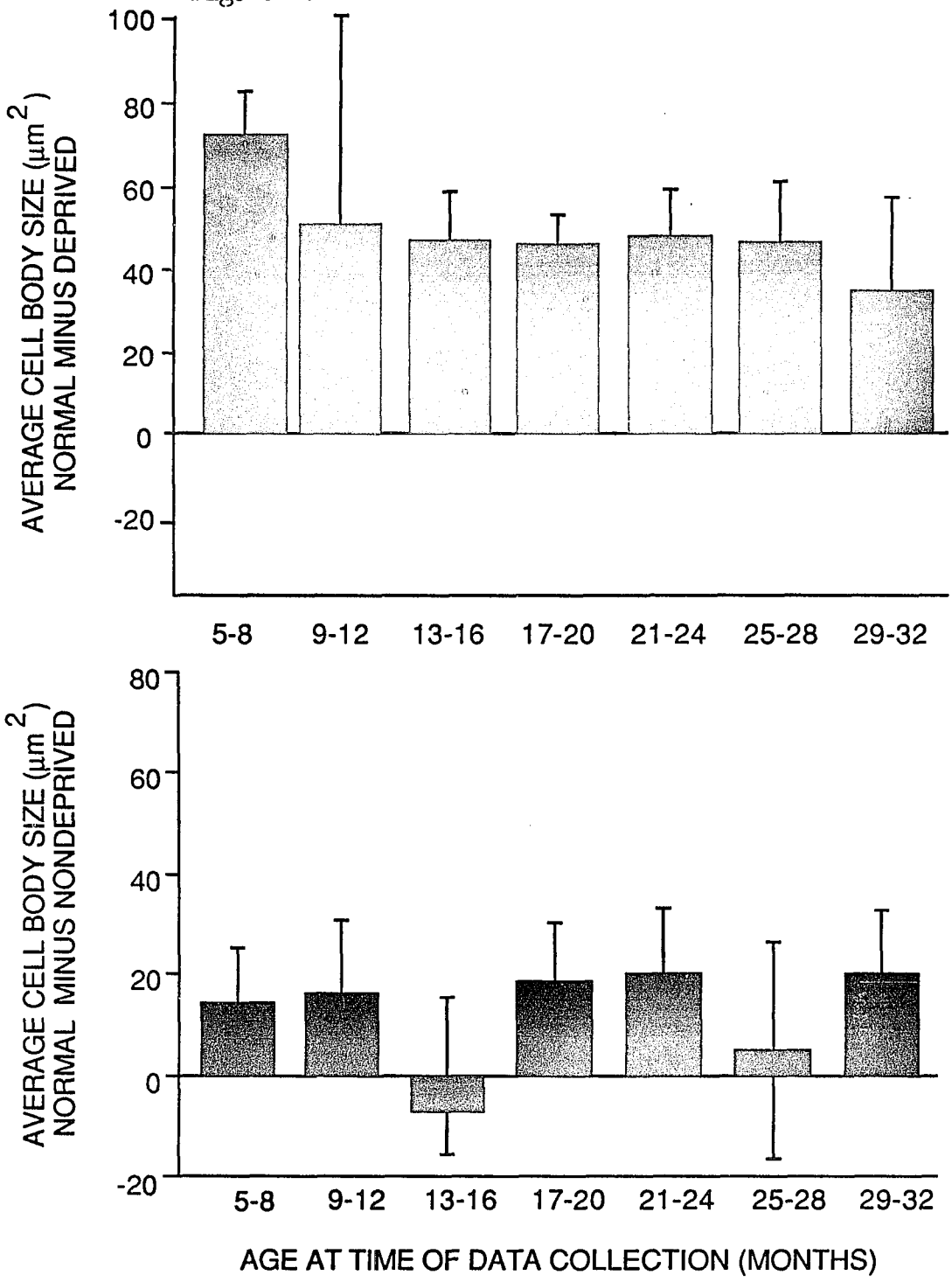
Figure 13a & b explores these possibilities by presenting the differences between normal values and the sizes of cells in the deprived and nondeprived laminae. As is evident in Figure 13a, the difference between average cell body size in the normal and deprived laminae diminishes with age and duration of lid suture. In Figure 13b it can be seen that the difference between normal and nondeprived laminae do not change over the age and duration of lid suture. Thus, most of the change in relative cell body sizes in the deprived and nondeprived laminae over time is accounted for by what appears to be a belated growth of cells in the deprived laminae. However, following a variety of comparisons, (normal minus deprived young versus old, M-W, $p > .10$; normal minus nondeprived young versus old, M-W, $p > .10$) we cannot distinguish between the three possibilities (deprived laminae cells are growing, nondeprived laminae cells are shrinking or both). Thus, visual deprivation initially yields a strong deprivation effect i.e., deprived laminae shrunken relative to nondeprived laminae. This morphological effect fades with the age and duration of lid suture in a manner parallel to, but not as complete as, the physiological effect.

Figure 13.

a. Bar graph showing the average cell size for subjects reared to various ages with kitten-onset lid suture. For each age bin the values for deprived laminae are subtracted from the normal mean cell body size value. The zero horizontal line indicates no difference between the two.

b. Bar graph as in 12a. except the average cell body sizes for the nondeprived laminae are subtracted from the normal mean. Symbols as in Figure 4.

Figure 13


AVERAGE CELL BODY SIZE (μm²)
NORMAL MINUS DEPRIVED
100
80
60
40
20
0
-20
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AVERAGE CELL BODY SIZE (μm²)
NORMAL MINUS NONDEPRIVED
80
60
40
20
0
-20
5-8
9-12
13-16
17-20
21-24
25-28
29-32
AGE AT TIME OF DATA COLLECTION (MONTHS)

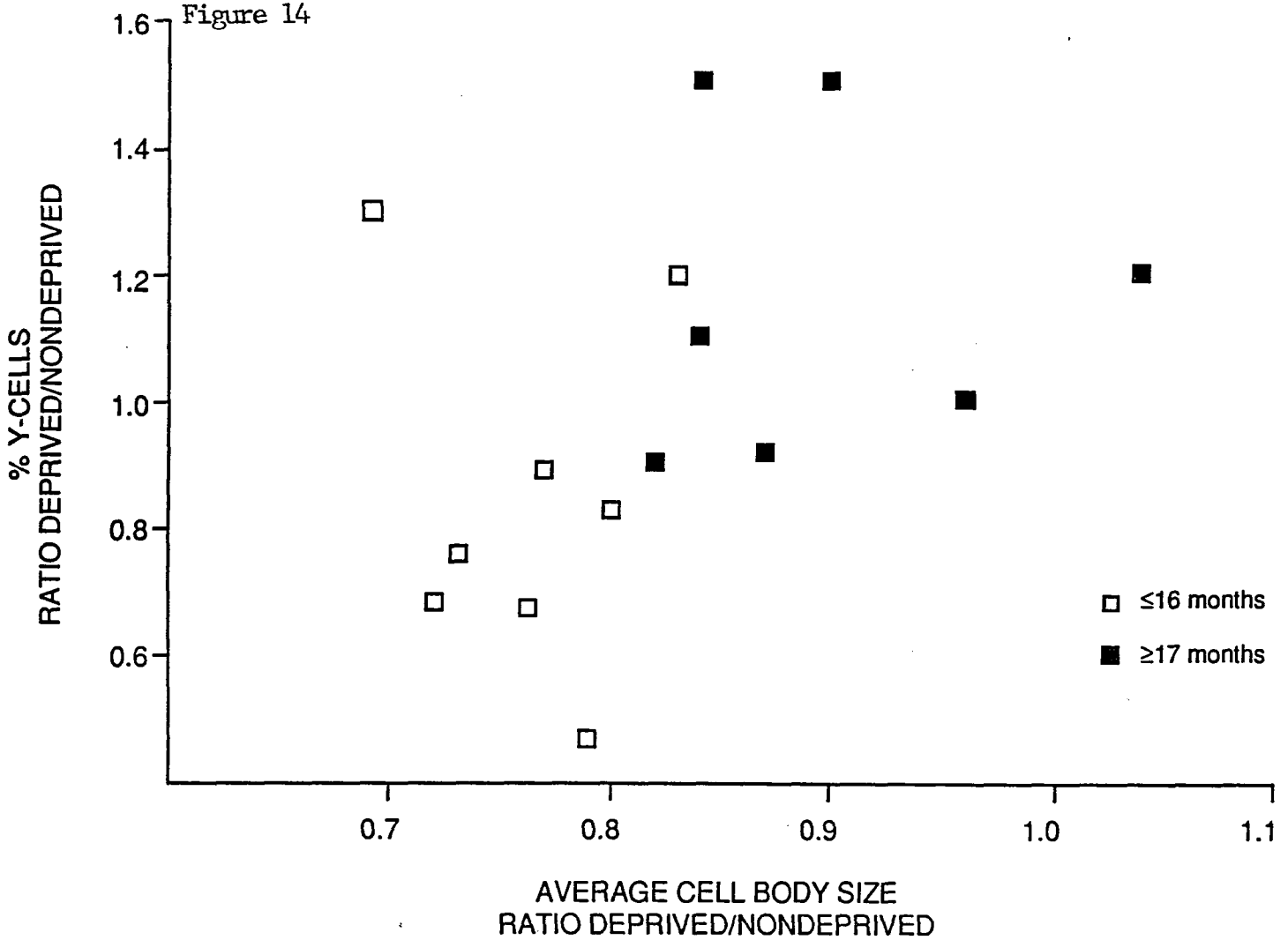
Physiological-Morphological Relationship

As stated above, visual deprivation yielded the morphological and physiological changes which were initially significant but which appeared to change direction with increasing age of the subject. To determine if the magnitude of the lid suture effects on Y-cell encounter rate and average cell body size covary, ratios were computed between the deprived and nondeprived morphological data and for the deprived and nondeprived physiological data. This approach permits the determination of the degree of correspondence by comparing the relative effects of deprivation on these two measures within each subject. These within-subject comparisons are illustrated in Figure 14. A test of the Spearman rank correlation between morphological and physiological effects of lid suture shows that for the subjects across all age groups, the correlation is significant ($r = 0.58$, $p < .02$). Thus, when the relative effects of deprivation on morphology and physiology within animals are compared, the effects of lid suture on X/Y cell ratios and average cell body sizes have a considerable degree of correspondence.

Another aspect of the data as presented in Figure 14 merits attention. Young subjects are represented by open squares and older subjects by closed squares. As is evident, the points representing the young and old subjects are segregated into separate groups (M-W,

Figure 14. A dot pattern illustrating the relationship between the morphological and physiological effects of lid suture within a single subject across different postnatal ages. On the abscissa are ratios determined by the percentage of Y-cells in the deprived and nondeprived laminae of individual subjects. On the ordinate are ratios made up of average cell body size data from the deprived and nondeprived laminae of individual subjects.

Figure 14


1.6
1.4
1.2
1.0
0.8
0.6
% Y-CELLS
RATIO DEPRIVED/NONDEPRIVED
0.7
0.8
0.9
1.0
1.1
AVERAGE CELL BODY SIZE
RATIO DEPRIVED/NONDEPRIVED
≤16 months
≥17 months

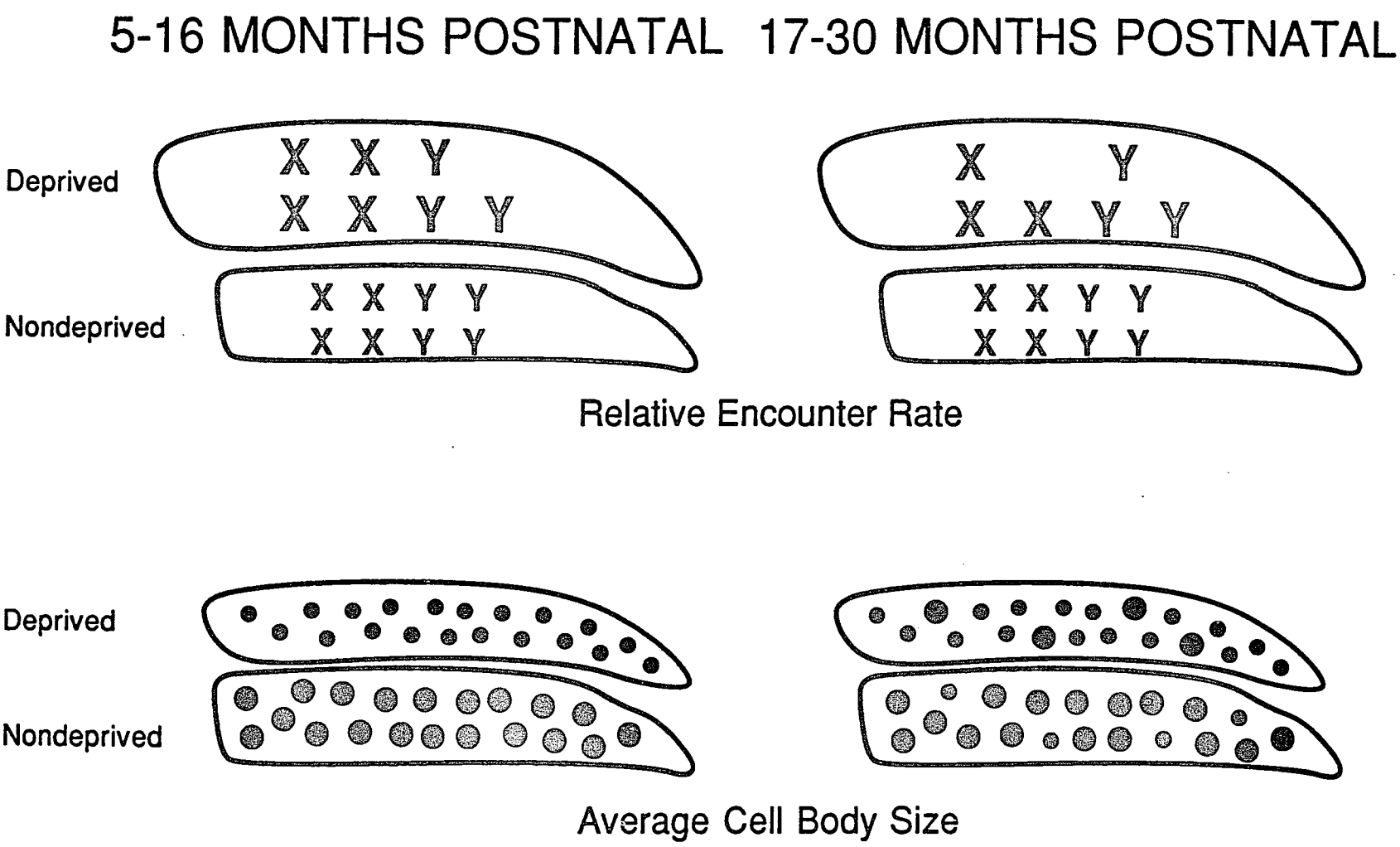
$p<.05$). This segregation indicates that there is a relationship between physiology and morphology; knowledge of the physiological and morphological consequences of deprivation in any given animal predicts with some degree of certainty which age group the subject was in at the time of data collection (i.e., young, < 17 mo. vs old, $\geq$ 17) (duration of deprivation). This implies that the influence of age and duration have an effect on the consequences of visual development even beyond the traditional "critical period".

These data represent several findings which are summarized in Figure 15. First, it was shown that when subjects are lid sutured at a single early age, the age at which a lid sutured animal is studied determines to a large degree the extent of the effect of visual deprivation even if all deprivation periods extend beyond the critical period. Thus, in younger subjects (< 17 months) a depressed percentage of Y-cells encountered was observed. However, subjects $\geq$ 17 months of age did not show this effect at all. That is, it appears as though the percentage of Y-cells was initially decreased by lid suture but then increased with increasing age and duration of lid suture.

Second, the morphological data showed that cell body size is reduced in the deprived laminae across all age groups. The difference between average soma

Figure 15. Schematic summary diagram which shows both the physiological (relative encounter rate for X- and Y-cells) and morphological (average cell body size) effects of short (5-16 months postnatal) and long (17-30 months postnatal) term lid suture.

Figure 15


5-16 MONTHS POSTNATAL
17-30 MONTHS POSTNATAL
Deprived
Nondeprived
X X Y
X X Y Y
X Y
X X Y Y
X X Y Y
X X Y Y
Relative Encounter Rate
Deprived
Nondeprived
Average Cell Body Size

size in the deprived relative to the nondeprived laminae appeared to reduce with age of the subject. No hypertrophy of cells was found in the nondeprived laminae.

Third, measuring both X-/Y-cell encounter ratio and cell body size in the same subjects revealed that in general these two measures both respond to lid suture. Furthermore, the degree of effect of lid suture on these two measures covaried within each animal. Therefore, the age of the animal, and thus the duration of deprivation, could be estimated from a knowledge of the ratios established between data from the deprived and nondeprived laminae.

CHAPTER IV

DISCUSSION

This chapter begins with a discussion of the electrophysiological findings in the present study along with various interpretations of these findings. Second, the morphological findings are treated in a similar fashion; a discussion of the results with interpretation. The third part examines the relationship, if any, between the physiological and morphological results. The subsequent two sections integrate the physiological and morphological findings of the present study along with other findings in order to explore mechanisms controlling recordability and soma size of dorsal lateral geniculate nucleus (LGNd) X- and Y-cells. Finally, the applicability of these results to the clinical situation is explored.

Physiology

Infant-onset lid suture resulted in a significant reduction in the encounter rate for LGNd Y-cells in the deprived laminae relative to the nondeprived laminae of cats 16 months of age or younger at the time of recording. This effect is consistent with previously reported studies of the effects of lid suture on development

which have shown "losses" of Y-cells in deprived geniculate laminae (Eysel et al., 1979; Garraghty et al., 1983, 1984; Geisert et al., 1982; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Kratz et al., 1978b; Mangel et al., 1983; Mower et al., 1981, 1985; Sherman et al., 1972, 1975; Sherman & Wilson, 1981; Zetlan et al., 1981). The magnitude of the loss found in the present experiment is small in comparison to some of these other reports. However, its small size is almost certainly attributable to the fact that only cells with receptive fields within the central 5 degrees of visual space were sampled since Mangel et al. (1983) have shown that the Y-cell loss following infant-onset lid suture is smallest in the area that represents the central 5 degrees of visual space. The fact that a statistically reliable reduction in Y-cell encounter rates was observed in the young subjects and was of an appropriate magnitude given the eccentricities sampled lends credence to the electrophysiological procedures employed in those animals and the data they provided.

In contrast to the findings in those "younger" lid sutured subjects, the Y-cell percentage found in the older lid sutured cats in the present experiment appeared to increase. Since the procedures used in the older animals were identical to those employed in the younger animals, the results from those older subjects

should be equally credible.

Even though the Y-cell percentage in the deprived laminae appeared to increase with increasing age of the subject past 17 months, it is not immediately obvious how this "recovery" should be interpreted. Three logical explanations exist: a Y-cell recovery, the superimposition of an X-cell loss, or some combination of the two.

Y-cell recovery? If the Y-cells have physiologically recovered, what could be the mechanism for recovery? A reevaluation of the fate of Y-cells in the infant-onset lid suture cats recorded at earlier stages of development could provide a clue as to the identity of the mechanism. Perhaps rather than being "lost" following visual deprivation, Y-cell development is simply retarded. It is known that the physiological development of Y-cells lags behind that of X-cells (Berardi & Morrone, 1984b; Daniels et al., 1978; Ikeda & Tremain, 1978; Norman et al., 1977). It has been suggested that since X-cells have an adult responsiveness soon after birth, they are impervious to visual deprivation whereas the immature Y-cells are more sensitive. This sort of delayed development has been demonstrated, for example, for cell body size in dark-reared cats where the cells eventually attain adult size, but at a rate somewhat slower than normal (Kalil, 1978a). If the physiological development of Y-cells in the LGNd was affected in a way similar to

the morphology in dark-reared cats, the Y-cells might also eventually mature, though more slowly than normal. This seems unlikely, however, because a physiological Y-cell loss is still evident even after the deprived eye is opened for some time (Hoffmann & Cynader, 1977; Sherman & Wilson, 1981; Wiesel & Hubel, 1965b). In fact, binocular exposure may actually exacerbate the effects of lid suture (Glass, 1980; Tumosa, Nunberg, Hirsch, & Tieman, 1983). This evidence, taken together, strongly suggests that it is unlikely that the normal relative Y-cell encounter rate in the older lid suture subjects can be explained by a lag in development of the Y-cells. This lag in development hypothesis would give the appearance of Y-cell recovery when in fact the Y-cells would have simply taken longer to develop.

Reversal studies involving exposing the deprived eye and closing the previously nondeprived eye also strongly suggest that the Y-cells which are "lost" after lid suture are not easily recovered. It has been shown that recovery can be produced, but only by dramatic measures such as opening the previously closed eye and removing or suturing the initially nondeprived eye (Geisert et al., 1982; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Hoffmann & Sireteanu, 1977; Spear & Hickey, 1979). Moreover, the "reversals" of the effects of lid suture obtained surgically (Geisert et al., 1982; Hoffmann

& Cynader, 1977; Hoffmann & Hollander, 1978; Hoffmann & Sireteanu, 1977; Spear & Hickey, 1979) or pharmacologically (Duffy, Snodgrass, Burchfiel & Conway, 1976) are never complete, while the Y-cell percentages in the older lid sutured subjects of the present experiment reach normal values. Because no additional environmental manipulation was imposed upon the older lid sutured subjects in the present experiment, it again seems unlikely that the Y-cells could have recovered in the deprived laminae with increased exposure to lid suture.

Even though evidence presented in the preceeding two paragraphs would seem to rule out the possibility of a Y-cell recovery in the older lid sutured subjects, it could be the case that more sensitive morphological procedures could detect a subtle sort of recovery in the Y-cells. That is, rather than cell body size, a more detailed study of dendritic structures or some other feature may show recovery. However, the kinds of morphological changes other than cell body size which have been reported to accompany deprivation (Friedlander et al., 1982; Garraghty, Sur, & Sherman, 1986; Sur et al., 1982; Tieman et al., 1984) seem sufficiently severe so as to preclude recovery of the sort seen physiologically in the deprived laminae of older lid sutured cats. That is, it has been reported that not only do the larger cells in the LGNd shrink, but the axons that innervate

them develop abnormally. Many of the retinogeniculate Y-axons from the deprived eye have dramatically shrunken or absent terminal fields (Garraghty, Sur, & Sherman, 1986; Sur, Humphrey & Sherman, 1982). Intracellular techniques have also shown major abnormalities in the structure/function relationships of LGNd Y-cells after lid suture (Friedlander, Stanford & Sherman, 1982). Thus, it seems that the morphological effects reported following lid suture are too great to allow a recovery of Y-cells, particularly when recovery is to have taken place during extended age and duration lid suture.

In summary, the three previous collections of data argue against a possible physiological return of Y-cells in the older lid sutured cats. Those who have attempted to stimulate a return of Y-cells by opening the deprived eye were unsuccessful (Hoffmann & Cynader, 1977; Sherman & Wilson, 1981; Wiesel & Hubel, 1965). Thus, allowing further aging with the deprived eye closed should not promote Y-cell recovery. Second, others who attempted to promote physiological recovery of the Y-cells by opening the deprived eye and either closing or removing the previously open eye were also largely unsuccessful (Geisert et al., 1982; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Hoffmann & Sireteanu, 1977; Spear & Hickey, 1979). Third, morphological changes other than cell body size have been reported which are quite

severe and which would seemingly not allow a physiological recovery (Friedlander et al., 1982; Garraghty, Sur, & Sherman, 1986; Tieman et al., 1984; Sur et al., 1982). These data in aggregate strongly suggest that the Y-cells in the older lid sutured cats did not recover physiologically.

X-cell loss? If a late appearing X-cell loss were superimposed upon an initial deprivation-induced Y-cell loss, one might observe what appears to be a normal X-/Y-cell ratio when in reality the physiology of cells in the LGNd is even more disrupted. The possibility of a late appearing X-cell loss in these cats which were reared with visual deprivation is supported by the fact that visual deprivation introduced in normally-reared adult cats has previously been shown to result in a reduction in the encounter rate for X-cells (Salinger, 1977a). Moreover, similar reductions in the encounter rate for X-cells have been demonstrated in normally reared cats after a wide variety of adult-onset perturbations (Garraghty et al., 1982; Salinger et al., 1977a, 1977b; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, Garraghty, & Schwartz 1980) justifying Salinger's early inquiry "Why does monocular paralysis of adults yield X-cell losses while visual deprivation of infants yields Y-cell losses?" (Salinger et al, 1978). Therefore, if lid suture or other adult deprivations generally

produce a loss of X-cells in adult cats, it is not unreasonable to suspect that such a loss might also be found in adult cats raised from infancy with eye lid suture.

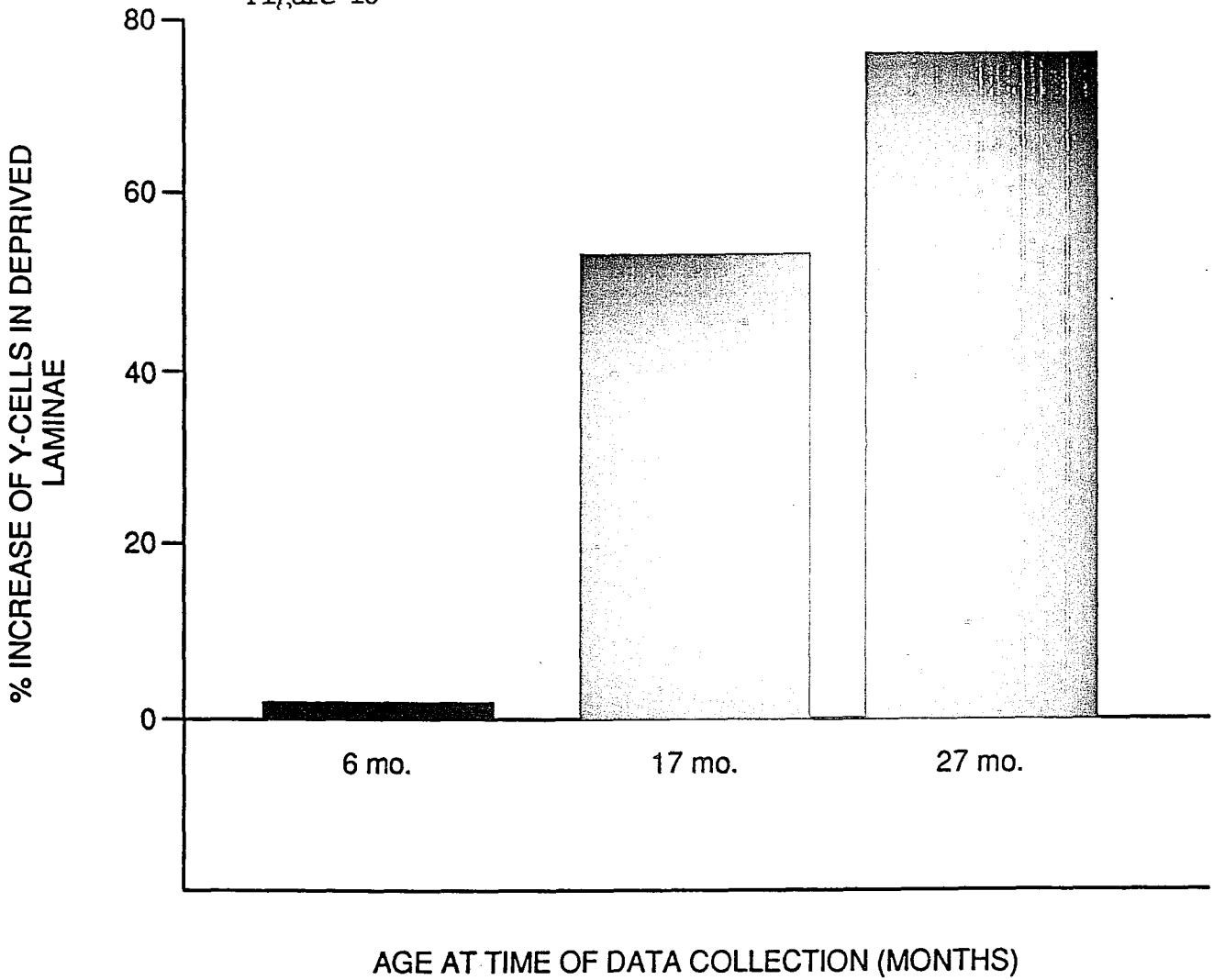
A preliminary test of the possibility of an X-cell loss in the older subjects hinges on the sensitivity of the adult effects to anesthesia. It has been previously reported that the loss of X-cells reliably observed in sedated subjects can be reversed in anesthetized preparations (Garraghty et al., 1982; Schroeder, 1985). The sensitivity of the adult LGNd X-/Y-cell ratio to levels of anesthesia during data collection has been well documented (Garraghty et al., 1982; Guido, 1986; MacAvoy & Salinger, 1982; Schroeder, 1986). This effect has been shown consistently across subjects and has even been reliably found between passes within a single subject (Guido, 1985; Schroeder, 1985). Therefore, if the normal percentage of Y-cells in the older subjects depends on an X-cell loss superimposed on a preexisting Y-cell loss in the LGNd, then anesthesia in the older subjects ought to reverse the X-cell loss, restoring the appearance of a Y-cell loss. A preliminary test of this idea in the present study supported this possibility by showing that the normal X-/Y-cell ratio in the older lid sutured subjects is sensitive to the effects of anesthesia during data collection. In contrast normal subject X/Y ratios are unaffected by anesthesia (Garraghty

et al., 1982; Schroeder, 1985). When older lid sutured subjects were anesthetized instead of sedated during data collection, they showed the same sort of Y-cell loss reported for the younger subjects. Importantly when these same subjects were sedated during recording, the normal X-/Y-cell ratio was found. Figure 16 displays the increase in encounter rate for Y-cells produced in three subjects in the anesthetized condition compared to their encounter rate during the sedated condition. The 6 month old subject showed a 2% change whereas the 17 month old showed a 53.5% increase and the 27 month old, a 76.7% increase in Y-cells from the anesthetized to the sedated state. This is consistent with a late appearing anesthesia sensitive X-cell loss from lid suture being superimposed upon on a Y-loss produced by early-onset lid suture. Of course in order to make a strong argument for the idea that the older lid sutured cats are sensitive to anesthesia because they have lost X-cells would require more data from both younger ($<$ 17mo.) and older ($\geq$17 mo.) lid sutured subjects.

This section covered two points which support the notion of an X-cell loss in the older lid sutured subjects. One, the finding of deprivation induced changes in X-cells of the adult LGNd is not a new one. Secondly, the anesthesia data although preliminary, also points to a loss of

Figure 16. Bar graph showing the effects of anesthesia in the deprived layers of one younger subject and two older subjects which were reared from 3-4 weeks postnatal with lid suture. This graph illustrates the percent increase in Y-cells in the deprived laminae from the anesthetized state to the sedated state within individual subjects.

Figure 16


80
60
40
20
0
% INCREASE OF Y-CELLS IN DEPRIVED LAMINAE
6 mo.
17 mo.
27 mo.
AGE AT TIME OF DATA COLLECTION (MONTHS)

X-cells rather than Y-cell recovery in the older lid sutured cats to explain the balanced X-/Y-cell ratio.

The apparent shift in X-/Y-cell encounter rates at 16-17 months

When kittens exceed 17 months of age, the Y-cells are encountered in increased proportions, presumably because an X-cell loss has been superimposed, whereas before this age a deficit in Y-cells is observed. This change in percentage of Y-cells confirms pilot observations, but perhaps the reality of this shift needs to be substantiated with further replication. Assuming for the moment that these results reflect an actual change in physiology, there are at least two ways that this change in physiology could occur. First, the X-cell suppression seen by 17 months could arise due to a gradual effect of deprivation on the brain or the X-cell system which, when it reached a certain threshold produces an X-cell loss. For example, deficits in the spatial acuity of X-cells have been noted in the deprived laminae of monocularly lid sutured cats (Hoffmann & Sireteanu, 1979; Lehmkuhle et al., 1978; Mangel et al., 1983). Importantly, these deficits in deprived X-cell spatial acuity were late-developing, first appearing at around six months of age (Mangel et al., 1983) and continuing in severity until about 15 months. Similarly, X-cell acuity deficits have been

reported in kittens reared with strabismus (Ikeda et al., 1977) and, in adult monocularly paralyzed animals, X-cells are suppressed. It seems possible that the reductions in spatial acuity of X-cells found by others in younger lid sutured or strabismic cats (e.g., Ikeda et al., 1977; Mangel et al., 1983) and the "loss" of X-cells found in the older lid sutured animals in the present experiment are due to the operation of a single mechanism. Perhaps, the mechanism which is initially responsible for the reduced spatial acuity continues to strengthen until some critical threshold is reached, after which the cells become undetectable, at least in the sedated state.

Second, the shift in physiology at 16/17 months of age could be due to growth-related changes in the organism. That is, growth-related changes in the subject could influence the onset of operation of the mechanism. For example, stereoacuity is influenced by changes in head size, more specifically interpupillary distance. Also, since the vertical horopter [theoretical surface in space which is everywhere equidistant from the two retinae (Ogle, 1932, 1950, 1962, 1964)] passes through the feet, binocularity must be affected by height as well. Since both height and interpupillary distance are changing until the organism reaches full physical maturity, it seems likely that the neural mechanisms

that must respond to their visual consequences would retain some form of plasticity until the subject reaches full physical maturity. However, it is unclear which of these variables is related to percentage of Y-cells. In the cat, the age for full maturity of stature is 16 months (Sobel, 1976) and hormonal changes needed to close sutures of the large bones could accompany the onset of physical maturity. If so, these hormones could act to change the vulnerability of neural connections to environmental influences. With or without the notion of neurohormones, a secondary plastic period in maturity could be postulated without denying the previously described critical period for development. The first critical period (i.e., for Y-cell development and ocular dominance segregation) begins at least by the time of natural eye opening (7-10 days postnatal) and ends abruptly by the end of the fourth month. The second, new form of plasticity (i.e., that postulated to account for the delayed loss of X-cells in the present experiment) begins at 17 months. At this time binocular anomalies yield this mature X-cell loss which may relect the development of a new or mature form of binocularity. This hypothesis must remain speculative for the moment and at most can be used to direct inquirey into neurohormones associated with this period in development. Alternatively, it could lead to attempts to find early and late maturing

strains of cats to see if these differing rates produce corresponding differences in the breakpoint between the first and second phases of response to deprivation.

The preceeding section addressed the physiological effects of long term lid suture. It was concluded that lid suture which is allowed to remain until beyond 17 months postnatal impacts on the X-cell system in addition to the Y-cell system. This additional consequence of lid suture could occur as a gradual effect on the X-cells which crosses a threshold for detection at about 17 months, or could be a sudden effect associated with the physical maturation of the organism.

Morphology

The morphological data collected in the present experiment are, at the first level of approximation, consistent with prior reports in the literature, in that visual deprivation consistently yielded some substantial soma size shrinkage. This is consistent with many other reports that cells in deprived LGNd laminae were found to be smaller than normal (Dursteler et al., 1976; Friedlander et al., 1982; Garey & Blakemore, 1977a, 1977b; Garey et al., 1973; Garraghty et al., 1984; Guillery, 1972, 1973; Hickey, 1980; Hickey et al., 1977; Hubel & Wiesel, 1970; Kalil, 1980; Kratz et al., 1978b; Kupfer & Palmer, 1964; Lin & Sherman, 1978; Movshon & Dursteler,

1976; Sherman et al., 1974; Wan & Cragg, 1976; Wiesel & Hubel, 1963, 1965). Therefore, the basic morphological effect of average cell size shrinkage in the deprived laminae which has been amply confirmed in the literature has been replicated in these subjects. This, together with the use of blind coded tissue samples in the present study, would validate the measuring procedures used here.

In some instances in the literature not only has a reduction in cell size in the deprived laminae been found, but also an increase in the average cell body size in the nondeprived laminae has been reported (Hickey et al., 1977). However this is not a consistent finding (Kalil, 1980; present results). This is important because the occurance of hypertrophy of cells in the nondeprived laminae has been used in support of notions of binocular competition in visual development and neural competition in development in the LGNd. No indication of hypertrophy was detected in the nondeprived laminae of either the young or old lid sutured cats in the present study. Kalil (1980) has also reported that nondeprived cells are not hypertrophic, and has suggested that Hickey et al. (1977) found hypertrophy because they used very young cats. That is, Kalil (1980) reported that the nondeprived cells of lid sutured cats grew at a faster than normal pace but, nonetheless, never exceeded adult

values. He suggested that Hickey et al. (1977) in studying cats as young as 3-4 months of age might have mistaken this accelerated growth for hypertrophy with respect to his normal age-matched controls. In any event, the present results give no indication of hypertrophy. Furthermore, the values obtained for both nondeprived and normal cells in the present experiment are in good agreement with previous reports of normal data (Garraghty et al., 1984, 1985; Guillery, 1966; Hickey, 1980; Hickey et al., 1977; Kalil, 1978a, b, 1980; Spear & Hickey, 1979).

While Kalil (1980) studied the effects of lid suture on the development of cell size over the first few postnatal months, the present experiment is the first to have assessed systematically this phenomenon over many months and even years. The present results show that while the classic visual deprivation effect remains evident in the older subjects, it becomes smaller until the magnitude of the difference between the average soma sizes in deprived and nondeprived laminae is small. That is, cells in the deprived and nondeprived laminae in the older cats are more nearly equal in size. The present results do not permit a resolution of the question of whether continued growth of cells in the deprived laminae, shrinkage of cells in the nondeprived laminae, or some combination of the two cause the reduction in

the difference between deprived and nondeprived cell size over time. That is, the effect is so small that it cannot tolerate the variability associated with between subject comparisons.

The convergence of the average cell body sizes in the deprived and nondeprived laminae which occurs in the older animals is provocative since it, as did the physiology, implies continuing responsivity of the nervous system to sensory disruptions in mature organisms. Several previous studies have demonstrated changes in LGNd cell size in adult cats with (e.g., Geisert et al., 1982) or without (Garraghty, 1984; Garraghty et al., 1982) a prior history of deprivation, so morphological changes of the sort found in the present experiment are not unprecedented. Those earlier demonstrations, however, all dealt with the introduction of some type of deprivation during adulthood, either reverse suture in cats raised with monocular lid suture (Geisert et al., 1982), or monocular paralysis in normally reared cats (Garraghty, 1984; Garraghty et al., 1982). In the present experiment changes in morphology were detected in the older animals relative to their younger counterparts even though no additional novel deprivation was imposed. Unfortunately, it is not possible to determine whether the morphology in the older animals represents the slow maturation of the nervous system after deprivation,

or the superimposition of a second effect, analogous to the addition of a postponed X-cell loss upon the pre-existing loss of Y-cells which may account for the physiology in these same animals.

In either event, the present results do not permit a resolution of the question of how the cell body sizes in deprived and nondeprived laminae in the older cats became less different as a function of age and duration of deprivation. Cells in deprived laminae could have become somewhat larger, cells in nondeprived laminae could have become somewhat smaller, or both of these changes could have occurred. It is important to note in this context that this change in morphology over time would have been undetectable had data from normal cats been used as controls. That is, relative to normal, cell size in the deprived laminae of both young and old subjects are abnormally small while cells in the nondeprived laminae are indistinguishable from normal. Only when the nondeprived laminae were used for control purposes, consequently controlling for between-animal variability, could the change in the deprivation effect on morphology in the older cats relative to the younger ones be detected. This finding illustrates yet again that care must be taken in the selection of appropriate controls (see, Garraghty et al., 1985; Sherman & Spear, 1982 for discussion of this issue).

Observations exist in the literature which could support either one or both of the changes which must have occurred in order for the deprived and nondeprived cells in the older cats to become less different in size. That is, cells in deprived laminae might have been expected to grow larger simply because their development had been slowed but not arrested by the lid suture. Such a slowing without arrest has been shown in cats deprived by means of dark-rearing (Kalil, 1978a; Mower et al., 1985). Alternatively, cells in the nondeprived laminae might have been expected to become smaller because of a recovery from an early hypertrophy (Kalil, 1980). Obviously, however, since no hypertrophy was detected in the nondeprived laminae of the younger subjects, this latter possibility is perhaps less tenable than the former. It is possible that since the changes between the young and old cats are relatively small, data from many more subjects might be required to detect a statistically reliable difference between the deprived or nondeprived laminae, or both. Alternatively, it is possible that the technique of intracellular recording and labeling with horseradish peroxidase (e.g., Friedlander et al., 1981) might reveal the nature of the changes occurring over time. Friedlander et al. (1982) noted substantial changes in the morphology of cells in the deprived laminae of lid sutured cats, but found cells

in the nondeprived laminae to be normal. Perhaps if these methods were employed in older cats, some recovery might be detected in cells in the deprived laminae or some defects might be observed in cells in the nondeprived laminae.

Correspondence Between Physiology and Morphology

The idea in the literature that Y-cell encounter rate and LGNd cell body size are somehow related, as seen above, was derived from observations in earlier studies that both were reduced in the deprived laminae of monocularly lid sutured cats (Friedlander & Stanford, 1984; Shapley & So, 1980; Sherman & Spear, 1982, for review). These physiological and morphological observations were not, however, made in the same subjects. In the present experiment, both sorts of data were taken from individual subjects to assess the extent to which a relationship exists at the level of individual subjects. Correspondence between these two factors has been demonstrated in the present experiment when the data from deprived laminae are viewed with respect to data from the nondeprived laminae of the same cats. By establishing within-subject ratios some degree of experimental error has been eliminated. Using this approach, fairly good agreement has been shown to exist between the physiological and morphological effects of lid suture in

individual subjects.

It is important to note, however, that when data from normal subjects were used for control purposes, rather than data from the nondeprived laminae, no such correspondence was apparent. While the use of within-subject controls for the purposes of assessing correspondence seems justified, the difference in outcomes, depending upon what serves as control data, points out once again that serious consideration must be given to this selection process (see Garraghty et al., 1985; Sherman & Spear, 1982).

The morphological and physiological data from the cats used in the present experiment were significantly correlated. When one realizes that the LGNd is comprised of perhaps 10 million cells of which only 200 or less are physiologically sampled and only 400 are morphologically sampled in each cat, the correlation is surprisingly high. As mentioned earlier, the existence of this correspondence had been previously suggested, but it had never been demonstrated in the same study, much less on an individual basis. The demonstration here that the morphological and physiological effects of lid suture are significantly correlated across individual subjects (when nondeprived data are used for control) apparently substantiates the belief which was derived from physiological and morphological data taken from separate groups

of animals. This powerful relationship could provide some clues as to the identity of the mechanisms responsible for the effects of lid suture and, furthermore, suggests that a common mechanism might be responsible for both effects.

There are at least two possible mechanisms which could account for the significant correlation between the physiological and morphological effects of lid suture shown in the present study. First, this correspondence could mean that one dependent measure is a passive consequence of the other. This would suggest that the regulation of cell body size and X-/Y-cell ratio are different manifestations of the same mechanism. The second possibility is that the morphological and physiological effects are caused by separate mechanisms, both of which can be engaged by the same mechanism.

Is the physiology a passive consequence of the morphology?

Recording Y-cell percentages in the LGNd has been used extensively to provide an index of "geniculate health". One must question, however, what a Y-cell percentage means and what controls the relative recordabilty of X- and Y-cells. Early in the history of the deprivation literature, it was suggested that the inability to record Y-cells in deprived geniculate laminae was due to their having shrunken to a size where they were no longer

detectable (see Shapley & So, 1980; Sherman & Spear, 1982 for review). That is, with all other things being equal, a given microelectrode will record large cells more easily than small ones. Such electrode sampling biases could, therefore, account for the physiological loss of Y-cells if the Y-cell somata were becoming too small to record (Shapley & So, 1980). It was subsequently demonstrated, however, that even though the larger [and, thus, Y-cell (Friedlander et al., 1981)] somata were preferentially affected by deprivation, they were still larger than the X-cell somata (LeVay & Ferster, 1977) which were recorded in normal numbers (e.g. Sherman et al., 1972). Further, as has been mentioned in another context, cell size in dark-reared cats is normal (Kalil, 1978a) even though Y-cells are physiologically lost (Garraghty, Frost, & Sur, 1986; Kratz, 1982; Kratz et al., 1979). Finally, as was also mentioned earlier, the encounter rate for LGNd Y-cells can be dissociated from average soma size by certain reversal manipulations. Thus, in cats reared with monocular deprivation, deprived soma sizes recover to normal values if the initially experienced eye is enucleated, but the encounter rate for Y-cells in the deprived laminae remains depressed (Geisert et al., 1982). If the initially deprived eye is then opened, a physiological Y-cell recovery is detected in the deprived laminae (Geisert et al., 1982). Clearly

the loss of Y-cells in these various conditions is not due merely to the fact that their somata have shrunken below the electrophysiogical limits of detection.

Similarly, after chronic monocular paralysis in normallyreared adult cats, soma size reductions are seen (Garraghty, 1984; Garraghty et al., 1982), and the electrophysiological encounter rate for X-cells is reduced (Garraghty et al., 1982; Salinger, et al., 1977b). Perhaps, since X-cells are smaller than Y-cells (Friedlander et al., 1981), a reduction in their size could result in an inability to detect their activity. It has been shown, however, that the "lost" X-cells recover physiologically in animals which are anesthetized during recording rather than merely sedated (Garraghty et al., 1982; Schroeder, 1985), and certainly changes in soma size cannot occur with such immediacy. Finally, a loss of X-cells has also been found after adult-onset chronic monocular paralysis (Garraghty et al., 1980; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger et al., 1977b) or monocular tenotomy (Salinger, Garraghty, MacAvoy, & Hooker, 1980) in geniculate laminae innervated by the non-operated eye. At least in the monocularly paralyzed subjects, however, no changes in soma size are detetable in laminae innervated by the mobile eye (Garraghty, 1984). The loss of X-cells in those laminae could not, therefore, be due to an inability to record

shrunken cells. It seems clear, therefore, that the recordabilty of X- and Y-cells in the LGNd is controlled by factors other than soma size. For example, Schroeder (1984) suggested that modulation of excitability in the LGNd is a major determinant for recordability of X- and Y-cells.

Is the morphology a passive consequence of the physiology?

The fact that the development of cell body size in the LGNd is disrupted by deprivation would seem to be beyond question. One can, however, speculate as to what changes in cell size reflect. One hypothesis which has been set forth historically to account for the control of cell body size is atrophy of disuse and is directly related to the physiological loss of Y-cells. That is, because the LGNd Y-cells are physiologically silenced, their somata shrink because of disuse much as muscles atrophy when paralyzed. This possibility is attractive in its simplicity, but numerous observations exist which demonstrate a lack of relationship between soma size and activity. For example, in cats reared in total darkness, Y-cells are lost (Garraghty, Frost, & Sur, 1986; Kratz, 1982; Kratz et al., 1979), but cell bodies develop to normal size (Kalil, 1978a). Furthermore, in cats which are reared with monocular lid suture into adulthood and then undergo enucleation of the non-deprived eye, the soma size of cells in the initially

deprived laminae are normal (i.e., have recovered from the effects of the lid suture), but Y-cells remain unrecordable. Only when the deprived eye is opened do the Y-cells in the deprived laminae become more recordable (Geisert et al., 1982). It seems very obvious, therefore, that the sizes of geniculate cells need not be determined solely by activity.

It appears reasonable to conclude that the mechanisms which regulate X-/Y-cell ratios and soma size can be independently stimulated. This conclusion is based upon the dissociations between the effects which are seen with certain rearing manipulations [i.e., dark-rearing (Garraghty, Frost, & Sur, 1986; Kalil, 1978a; Kratz, 1982; Kratz et al., 1979)] and with all adult-onset manipulations whether preceded by normal development (Garraghty, 1984; Salinger et al., 1977b) or not (Geisert et al., 1982).

Mechanisms Controlling Recordability of X- and Y-cells

The fact that X- and Y-cells in the LGNd can be "lost" to recording following any number of visual sensory perturbations is beyond doubt. One can speculate about whether the mechanisms controlling the recordability of these two cell classes are the same. For example, Schroeder (1984) has shown that under certain circumstances the relative encounter rates for X- and Y-cells can be made to change in equal but opposite directions (also

see Garraghty et al., 1982). This complementarity in relative excitability suggests that there are at least some situations where the recordability of the two cell classes is related. Other examples exist, however, which show that changes in the encounter rate of one cell type can occur with no changes in the other. For example, the Y-cell loss in lid sutured cats is not accompanied by an increase in X-cells (Sherman & Spear, 1982). Just as with the earlier comparison between soma size and encounter rates for X- and Y-cells, it seems most likely that the relative recordability of these cell classes can be controlled by separate mechanisms.

This latter conclusion receives strong support from general conclusions which can be drawn from the literature and the present study. First, deleterious effects on Y-cells are found only after infant-onset perturbations. Thus, infant-onset lid suture (Eysel, et al., 1979; Garraghty et al., 1983, 1984; Geisert et al., 1982; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Kratz et al., 1978b; Mangel et al., 1983; Mower et al., 1981, 1985; Sherman et al., 1972, 1975; Sherman & Wilson, 1981; Zetlan et al., 1981), strabismus (Ikeda et al., 1977; Ikeda & Tremain, 1978), dark-rearing (Garraghty, Frost, & Sur, 1986; Kratz, 1982; Kratz et al., 1979; Mower et al., 1981, 1985) and monocular paralysis (Salinger et al., 1978) all result in effects

on the Y-cell system. In no instance has a suppressive effect on Y-cells been found after the introduction of a manipulation in a normally developed adult. Second, X-cells are often affected by adult-onset perturbations in normallyreared cats. Thus, adult-onset monocular paralysis (Garraghty et al., 1982; Salinger, Garraghty, & Schwartz, 1980; Salinger et al., 1978b), binocular paralysis (Salinger, Wilkerson, & MacAvoy, 1977; Wilkerson, Salinger, & MacAvoy, 1977), monocular tenotomy (Salinger, Garraghty, MacAvoy, & Hooker, 1980) and binocular deprivation (Salinger et al., 1977a) all result in selective suppression of recordability of X-cells. Finally, although the results of the present experiment suggest that effects of anesthesia need to be assessed systematically in both short- and long-term lid sutured cats, these preliminary anesthesia data in conjunction with others show that the mechanisms underlying the early loss of Y-cells and the late loss of X-cells are differentially affected by anesthesia. That is, the reduced encounter rate for Y-cells is not sensitive to manipulations in anesthesia (present study; Geisert et al., 1982; Hoffmann & Cynader, 1977; Sherman et al., 1972; Sherman & Wilson, 1981) whereas X-cell recordability is (present study, Garraghty et al., 1982; Schroeder, 1984). It is possible to once again speculate on the age-related differential sensitivities of X- and Y-cells in the wake of these observations.

Y-cells. The initial report of the effects of lid suture on Y-cells stressed the selectivity of the effect (Sherman et al., 1972). Why should lid suture in infancy have such an immediate and dramatic effect on only one class of visual cells? As described earlier, the physiological development of Y-cells generally lags behind that of X-cells (Berardi & Morrone, 1984; Daniels et al., 1978; Ikeda & Tremain, 1978; Norman et al., 1977). Moreover, their morphological development also shows this difference. Thus, relative to Y-cells, X-cells are apparently born earlier in the retina (Rapaport & Stone, 1983; Stone et al., 1982; Walsh et al., 1983), have axons which enter the optic tract earlier (Walsh et al., 1983), have well-elaborated axonal arbors in the LGNd earlier (Sur et al., 1984), and develop normal LGNd soma sizes earlier (Kalil, 1980). The most parsimonious explanation for the nonspecific effect of deprivation on Y-cells after early deprivation would be namely that the Y-cells are relatively more vulnerable because of their relative immaturity and consequent rapid growth. However, it remains possible that an explanation involving a specific deprivation effect may be that normal visual experience is required for their development. In either case, it is important to stress that if permitted to develop normally, the Y-cell system is apparently impervious to later-commencing manipulations.

Even though the effect of early perturbations on Y-cells is a reliable finding, the mechanism which produces this loss remains obscure. One possibility which is attractive in its simplicity is the quality of synaptic linkage. For example, the deprived retinogeniculate Y-cell axons of lid sutured cats fail to develop (Garraghty, Sur, & Sherman, 1986; Sur et al., 1982). It seems very possible, therefore, that Y-cells in the LGNd are not physiologically detectable because they have an insufficient amount of retinal input. Evidence counter to this possibility is available, however, in dark-reared cats: in those cats, LGNd Y-cells are lost physiologically (Garraghty, Frost, & Sur, 1986; Kratz, 1981; Kratz et al., 1979), but retinogeniculate Y-cell axons are normal in all aspects of their appearance at the light microscope level (Garraghty, Frost, & Sur, 1986). It seems more parsimonious to conclude, therefore, that LGNd Y-cells are not lost in the deprived laminae of lid sutured cats merely because of insufficient retinal drive.

Another possibility is that the loss of the deprived eye's capacity to drive cells in visual cortex exerts some retrograde effect on geniculate Y-cells which renders them less excitable. In the cortex of monocularly lid sutured cats, the nondeprived eye is dominant physiologically and morphologically (see Sherman & Spear, 1982 for review). It seems possible that the functional activity of Y-cells

in the deprived geniculate laminae could then be suppressed, perhaps via corticofugal pathways mediated by the dominant eye. Differences in the magnitudes of effects of monocular and binocular deprivation certainly seem to suggest a role for binocular competition (Sherman & Spear, 1982). Furthermore, Y-cells in deprived laminae can be made to recover by both providing visual input by opening the lid sutured eye and eliminating any obvious opportunity for competitive interactions by enucleating the early-experienced eye (Geisert et al., 1982). This observation also supports the contention that some form of binocular suppression is involved in the Y-cell losses after infant-onset manipulation. Again, however, observations from dark-reared cats seem to counter this possibility. In dark-reared cats, neither eye dominates in cortex (Mower et al., 1985; Swindale, 1981), so a competitive imbalance at that level does not exist. Yet the magnitude of the loss of Y-cells in the LGNd is as severe as that seen in the deprived laminae of monocular lid sutured cats (Kratz et al., 1979; Sherman & Spear, 1982) in which competitive imbalances do exist in cortex. Furthermore, it has been demonstrated that the Y-cell loss after monocular deprivation is not reversed by lesions of visual cortex (Zetlan, Spear, & Giesert, 1981). Therefore, while corticofugal influences might still play some role in the generation of the Y-cell loss,

they certainly are not responsible for its maintenence. It would appear, therefore, that the status of binocular competitive interactions in cortex alone is not causally related in any simple and direct fashion to the loss of Y-cells in the LGNd.

It is possible, however, that lid suture and dark-rearing differ in a fundamental way. Perhaps the loss of Y-cells in dark-reared cats reflects a true and complete failure in Y-cell development. That is, it is possible that the amount of light which can be transmitted through the closed lids of sutured cats is sufficient to stimulate the initiation of the process of Y-cell physiological maturation but not sufficient to permit this maturational process to proceed normally. In contrast, in darkreared cats with no light comming in, development is simply not begun. In this view, some light is necessary to initiate Y-cell development, but normal patterned vision is necessary in order for normal development to occur. This reasoning must remain speculative at present, but it may prove possible to test this hypothesis by studying recovery in dark-reared and binocularly sutured cats. As mentioned above, Y-cell recovery can be induced in monocularly lid sutured cats by appropriate manipulations involving the provision of visual input and the elimination of competitive imbalances by enucleating the experienced eye. Because such competitive imbalances would not

exist (at least not as severely) in dark-reared and binocularly lid sutured cats, it seems reasonable to suppose that simply providing visual inputs might be sufficient to stimulate a Y-cell recovery. It is known, however, that extensive (i.e., up to two years) normal visual exposure following dark-rearing has no ameliorative effect on Y-cell encounter rates (Kratz et al., 1979). Unfortunately, comparable data do not exist for binocularly sutured cats, but perhaps Y-cells in such cats could recover after extended visual exposure following the period of deprivation. In summary, it is not yet clear by what mechanism Y-cells are rendered unrecordable following deprivation, but is is unquestionable that this mechanism has substantial power in the early developing months of the organism to reduce the electrophysiological recordability of Y-cells.

X-cells. Unlike Y-cells, X-cells are reliably affected by adult-onset manipulations in the normally-reared adult cat. Salinger and colleagues (Brown & Salinger, 1975; Garraghty, Salinger, MacAvoy, Schroeder, & Guido, 1982; Guido, 1985; Guido, Salinger, & Schroeder, 1984; MacAvoy & Salinger, 1980; Salinger, 1977; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, Guido, & Schroeder, 1984; Salinger, Schwartz, & Wilkerson, 1977a, b; Salinger, Wilkerson, & MacAvoy, 1977; Schroeder, 1985; Wilkerson, Salinger, & MacAvoy, 1977) reported

changes in the relative encounter rate for X-cells in the adult LGNd following a variety of adult-onset visual stimulus modifications, and have suggested that chronic monocular paralysis reduces the relative encounter rate for X-cells due to the activity of a mechanism sensitive to binocular disruptions. The facts that (1) chronic monocular paralysis reduced the X-cell encounter rate in both the contralateral and ipsilateral LGN's, and in all of the principal laminae whether the innervating eye was paralyzed or mobile (Garraghty et al., 1982), (2) the effects of chronic monocular paralysis are confined to portions of the LGNd representing central visual space, and (3) and that the stimuli important for the X-cell loss are inherently binocular, i.e., abnormal patterns of retinal disparity and oculomotor asymmetry (Salinger et al., 1980a,b), clearly lent credence to this hypothesis. Importantly, it was suggested that this reduced encounter rate for X-cells was due to a tonic inhibition rather than that the cells were lost or shriveled beyond the limits of electrophysiologic detection (Garraghty et al., 1982). This conclusion was supported by the fact that when the subjects were anesthestized rather than sedated during data collection, the encounter rate of X-cells relative to Y-cells in the chronic monocular paralysis animals was restored to normal proportions (Garraghty et al., 1982; Schroeder

1985). It was further shown that when level of anesthesia was altered during data collection this X-/Y-cell ratio shift in favor of the X-cells could occur rapidly (Schroeder, 1984). The fact that the effects of chronic monocular paralysis are so easily reversible also suggests that the losses of X-cells in adult cats and Y-cells in infant cats are due to separate mechanisms.

The evidence reported above supports the idea that although they may be related at some level, the mechanisms controlling recordability are unique to each cell class. The mechanisms differed in at least two respects. First, X-cells are affected in normally reared adults whereas no changes in the Y-cell system has been shown in normal adults. That is, Y-cells are sensitive to environmental modification early in development whereas X-cells are affected much later. Second, X-cell recordability is quite sensitive to level of anesthesia whereas Y-cell recordability has not shown this sensitivity.

Is a single mechanism responsible for the loss of X-cells in normally reared adults and adults reared with lid suture?

We are now left with the question of what could the mechanism be which controls the recordability of LGNd cells in older lid sutured subjects in the present study. The present results, combined with previous

reports of X-cell losses following adult-onset visual disruptions, chronic monocular paralysis in particular, could shed some light on this issue. The mechanisms underlying the effects of chronic monocular paralysis (CHMP) have been extensively studied. Therefore, comparisons between this paradigm and long term lid suture could suggest possible mechanisms operating with long term lid suture.

In order to suggest ways in which mechanisms for the effects of longer term lid suture might have properties similar to those which have been suggested to operate for adult-onset CHMP, it is necessary to determine the relationship, if any, between the two. One way in which they are similar is that both paradigms are sensitive to the effects of anesthesia. That is, when both older lid sutured (based on preliminary data presented here) and CHMP subjects are anesthetized during data collection, the previously missing X-cells become electrophysiologicaly recordable. Thus the mechanism(s) controlling X-cell recordability in both deprivation paradigms are pharmacologically sensitive in a comparable way.

Recent work involving the electron micrographic serial reconstruction of single physiologically identified LGNd relay cells (Wilson, Friedlander, & Sherman, 1984) have identified the structure and sites of synaptic contacts upon physiologically identified geniculate

X- and Y-cells. This work has shown that the sites and synaptic structure and different for X- and Y-cells. Prior work at the electron microscopic level has shown that excitatory and inhibitory synapses can be distinguished on the basis of synaptic vesicle morphology. These data together, therefore, permit one to understand the interplay of excitation and inhibition impinging on individual LGNd neurons. Not surprisingly, the potential sources of inhibition (extraretinal facilitation and/or disinhibition) are limited by this synaptology, as are the pathways which might respond to anesthetics. The limited number of inhibitory pathways and the similarity of their response to anesthesia certainly suggests that the X-cell losses which accompany both long term lid suture and CHMP arise from the operation of a common mechanism.

While the mechanism may be identical in the two cases at the cellular level, however, its operation at the systems level is clearly different. That is, both after infant-onset lid suture in the older subjects and CHMP, LGNd X-cells are lost, but this reduction in encounter rate for X-cells after lid suture occurs only in the deprived laminae. After CHMP on the other hand, this reduction occurs across all laminae of the LGNd whether innervated by the paralyzed or mobile eye.

Why should the laminar pattern of effects differ between the two paradigms? The pattern of effects could differ because the stimuli which are disrupted by each of these deprivations are different. That is, during monocular paralysis there is an active disruption of the visual scene. Both eyes are open and with one eye unable to move with respect to the other, two different views of the visual environment are produced. Garraghty et al. (1982) suggested that this sort of abnormal pattern of retinal disparity and ocular asymmetry, which produces competition between images on the retina, triggered the binocular mechanism operating to actively suppress X-cells after CHMP. During lid suture a different set of stimulus modification occurs, a reduction in illumination coupled with a lack of pattern vision. Thus, from a visual stimulus perspective, CHMP disrupts an actively binocular mechanism, whereas with lid suture this is not necessarily the case.

Because the mechanisms operating to differentiate long term lid suture from the shorter durations in CHMP seem to share the same pharmacological pathway, i.e. elements sensitive to the same anesthesia and neurotoxins, it seems likely that the mechanism operating in older lid sutured subjects could at least in part be identical to the mechanism operating in the young lid sutured subjects. These common elements however must affect

different secondary elements which could thus produce the differential effects for infant-onset deprivations which last into adulthood compared to adult-onset monocular paralysis.

Mechanisms controlling LGNd soma size

As was discussed previously, LGNd soma size does not reflect the operation of something as simple as atrophy of disuse. Another hypothesis which has been proposed to account for LGNd soma size relates this morphological feature to the size of the cells' axonal arbors in cortex. That is, cells with larger axonal arbors might presumably require larger somata to contain all of the additional metabolic mechinery necessary for the maintenance of the larger arbors. Good correspondence has been demonstrated between these two aspects of cellular morphology (see Garraghty et al., 1985; Movshon & Van Sluyters, 1981 for brief reviews).

This hypothesis states that during development axons arising from cells in geniculate laminae innervated by the two eyes compete for synaptic space in cortex. In the immature kitten, the arbors of axons serving the two eyes overlap extensively in cortex, and during the first few months of life, if visual experience is balanced, these arbors retract somewhat (Hubel & Wiesel, 1977; LeVay et al., 1978). The resulting pattern of

segregation based upon ocular dominance is characterized by stripes or bands with alternating left eye and right eye domains. When one eye is sutured early in life, the normal competitive balance between the two eyes is disrupted. The experienced eye is placed at a competitive advantage, and as a result of this advantage, it comes to dominate cortex both anatomically (Shatz & Stryker, 1978) and physiologically (Wiesel & Hubel, 1963b). The visually deprived eye, on the other hand, maintains a much sparser anatomical connectivity with cortex and can drive very few cells. This pattern of cortical effects of monocular lid suture can readily account for the geniculate morphology. That is, the cells whose arbors have been decimated because of the competitive imbalance (i.e., the cells in deprived geniculate laminae) are much smaller than normal because they need very little metabolic machinery to maintain these abnormally sparse arbors.

This hypothesis can also account for data from experiments involving other rearing paradigms. For example, in cats which are reared in the dark, unbalanced binocular competitive interactions are not possible. In such cats, ocular dominance columns form (Swindale, 1981; Mower et al., 1985; Stryker & Strickland, 1986), and, as mentioned previously, LGNd cell sizes develop to normal levels (Kalil, 1978a). Furthermore, if dark-reared

cats are permitted occasional monocular visual exposure, with each eye receiving equal amounts of patterned stimulation (equal alternating monocular exposure), thinner ocular dominance columns form because of abnormally sharp borders (Hubel & Wiesel, 1965; Tumosa & Tieman, 1981). That is, the normally-occuring zones of transition between adjacent ocular dominance columns are absent or much reduced. In parallel with this relatively minor abnormality in cortex, LGNd cell sizes are somewhat smaller than normal (Tieman, Nickla, Gross, Hickey, & Tumosa, 1984), though not nearly so small as cells in the deprived laminae of monocularly lid sutured cats (see Sherman & Spear, 1982). Finally, in cats reared with strabismus, geniculocortical afferents serving the two eyes are again found to be more clearly segregated than in normal cats (Shatz, Lindstrom, & Wiesel, 1977), and cells in the LGNd are apparently smaller than normal (see Garraghty, 1984, Garraghty et al., 1985). It appears, therefore, that the hypothesis relating LGNd soma size to geniculocortical afferent geometry is powerful, and, indeed, to date, no examples of dissociations between these morphological features have been reported.

Given the validity of the LGNd soma size-cortical arbor hypothesis, one can speculate about the implications of the data from the present experiment for geniculocortical circuitry. In the young cats, a large disparity existed

between the sizes of cells in the deprived and nondeprived laminae. Presumably, this disparity reflected the dominance of the experienced eye's afferents in cortex and the sparseness of the deprived eye's connections. With increasing age, the present experiment has shown that the difference between deprived and nondeprived laminae cell sizes was reduced. If LGNd soma size does in fact reflect geniculocortical axonal arbor size, then this result can only mean that deprived eye arbors are becoming larger and experienced eye arbors are becoming smaller in the older cats. While it might be difficult to demonstrate this change anatomically at the level of cortex, it would be a most impressive demonstration because it has been widely assumed that geniculocortical circuitry is relatively immutable at the close of the so-called critical period for visual system development (Hubel & Wiesel, 1970; Mower et al., 1985).

Perhaps the morphological changes in the older cats involve a process analogous to the hypertrophy which may be transiently present in the nondeprived laminae of lid sutured cats (Hickey et al., 1977; Kalil, 1980). That is, if hypertrophy of LGNd cells reflects abnormally large cortical arbors, then the return of more normal soma size later in development would reflect some pruning of the axonal arbor. It is possible that the early failure of many nondeprived axons to retract

normally results in axonal arbors which are so abnormally large that they exceed the upper limit established by the cells' genetic capacities. An example of this sort of genetic limitation is available for retinogeniculate axonal arbors.

Early in postnatal life, as retinogeniculate X- and Y-cell axonal arbors begin to establish their mature morphologies in the LGNd, these two cell classes differ greatly. In the 3-4 week old kitten X-cell arbors in the LGNd are found to be much larger than in the normal adult while the opposite is true for the Y-cell arbors (Sur, Weller, & Sherman, 1984). As the animals mature, the X- and Y-cell arbors reach their adult morphologies (Bowling & Michael, 1984; Sur & Sherman, 1982) via retraction and growth, respectively. This observation led to the formulation of the hypothesis that X- and Y-cell axons from a single eye compete for synaptic space in the LGNd in much the same way that afferents from the two eyes compete in cortex (Garraghty, Sur, & Sherman, 1986; Garraghty, Sur, Weller, & Sherman, 1986; Sur et al., 1982, 1984). In this view, the initially exuberant X-cell axons are pruned because the later-growing Y-cell axons enjoy a competitive advantage for those synaptic sites from which the excess X-cell axons terminations are displaced. Support for this hypothesis has been provided by several experiments. First, in cats reared

with monocular lid suture, X-cell axons in the deprived laminae are able to retain their youthful exuberance while deprived Y-cell axons fail to develop (Sur et al., 1982), presumably because the later-growing Y-cell axons are placed at a competitive disadvantage by the lid suture. Similarly, in cats reared with one eye removed, X-cell axons from the remaining eye are again found to have retained their youthful exuberance, but in this instance, not at the expense of the later-maturing Y-cell axons (Garraghty, Sur, Weller, & Sherman, 1986). Rather, the Y-cell axons form abnormal translaminar sprouts into adjacent denervated layers, possibly because they find this to be a less resistent path for growth than competitively displacing the exuberant X-cell axons in the normal target layer (Garraghty, Sur, Weller, & Sherman, 1986). Finally, the important experiment for the present discussion involved cats reared with one eye enucleated and the other lid sutured. In this context, one might expect X-cell axon arbors to be larger still since they both enjoy the competitive advantage associated with the lid suture and are relieved from competive pressure because of the alternate path for Y-cell axon growth grovided by the enucleation. In these cats, however, even though Y-cell axons sprout into dennervated territory and fail to develop normally in the visually deprived target laminae, the X-cell

arbors are no larger than in juvenile, lid sutured, or monocularly enucleated cats (Garraghty, Sur, & Sherman, 1986). It would seem, therefore, that the largest sizes that any single X-cell axon arborc an maintain is ultimately determined intrinsically. The same may well be true for the geniculocoritcal axonal arbors in the older cats in the present study. Perhaps in the younger cats, the geniculocortical axonal arbors from the nondeprived laminae have a reach which exceeds their grasp so that their possibly smaller size in the older cats reflects the maximum which can be permanently maintained. Growth on the part of deprived geniculocortical afferents in the older animals might then reflect a relatively passive response to the availability of exposed terminal sites as the nondeprived afferents retract to their maximum allowable size.

Clinical implications

There has been a renewed interest in amblyopia in the past several years as indicated by the increased volume of literature devoted to this visual system disorder. Amblyopia is a condition that is characterized by reduced visual function and is thought to be due to a failure of early visual central nervous system development (Hess, 1984) which afflicts about 5% of people (Marg, 1982). Although the specific time frame differs among organisms,

for comparable deprivation conditions, knowledge of the deprivation effects in one species (subhuman primate, cat, human) seems to inform one of the deprivation effects in the other species (Marg, 1982, Odom, 1983, Von Noorden, 1979). For example, eye closure in kittens is a good animal model for cataracts (lens opacity), ptosis (drooping of the eyelid), or hemangioma (a type of congenital vasuclar tumor in the eyelids in which either large veins or capillaries become engorged with blood causing the lid to enlarge and therefore occlude vision (Vaughan & Asbury, 1980) in humans (Odom, 1983).

Lid suture in cat has been widely used as a model of amblyopia. This model of form deprivation amblyopia has contributed significantly to our understanding of visual system development as well as to the clinical conditions. Previously, it had been suggested that changes in the Y-cell system during the early "critical period" (first 3 months postnatal) are important in the development of deprivation amblyopia. Attempts at reversing this early effect surgically (Geisert et al., 1982; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Hoffmann & Sireteanu, 1977; Spear & Hickey, 1979) or pharmacologically (Duffy et al., 1976) have been partially successful. This reversal literature suggests that a lot of the basic neural machinery may be present and capable of responding correctly but, for some reason,

functionally disordered. At least for the initial stages of the visual process such a state of affairs could be thought of more in terms of an active "neural interference" within the amblyopic visual system rather than the more traditionally accepted view of neuronal loss.

However, reversals in visual perceptual abilities have not been so successfully accomplished (Mitchell, 1983). This suggests that the brain may have at least two neurodevelopmental mechanisms with which to cope with visual form deprivation. One mechanism may involve partial elimination of the input from the eye receiving abnormal visual stimulation, during the early Y-cell pathway critical period. The other mechanism may involve a partial elimination of the input from the X-cell pathway during a later critical period.

The present study has elucidated this important aspect of environmental influences and the function of the X- and Y-cell pathways. The effects of lid suture on the X- and Y-cell systems are different both in terms of type and developmental timing. The deficits in the Y-cell system emerge during the period of rapid growth for this system and occur only when the deprivation is induced during the traditional critical period, the first 3 months of postnatal life. The deficits in the X-cell system emerge later with a decrease in the spatial resolving power of LGNd X-cells beginning at about six

months and continuing in severity until about 15 months postnatal. The present study has pointed to an additional previously unreported deficit, apparent suppression of X-cells following long term infant-onset lid suture. This previously unreported deficit is first evident at about 17 months postnatal age or after 16 months of deprivation. At what developmental age this X-cell deficit would be seen in humans is an important question. Perhaps it could correspond to the age at which an additional hitherto undescribed adult-onset effects of amblyopia appear. No studies of human amblyopes exist which compare symptoms in juveniles and adults. For example, in humans it has been suggested that the treatment of amblyopia should begin not later than 2 years of age and it is progressively harder to treat after the age of 5, especially after age 7 or 8 (Marg, 1982). Perhaps the progressive increase in the difficulty of treatment reflects the beginning of damage to the X-cell pathway.

In conclusion, it has been suggested that when comparing animal models of amblyopia to the human condition, it is important to choose the appropriate deprivation paradigm. In addition, to understand fully the underlying neurological status of the amblyope, it is important to take into account the developmental age of the experimental animal to which it is compared rather than just the experimental manipulation to which this animal has

been exposed.

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Appendix A

Creysl Violet stain for revealing Nissl substance*

1.	70% ETOH**	3 min.
2.	80% ETOH	3 min.
3.	90% ETOH	3 min.
4.	100% ETOH	3 min.
5.	Xylenes	15 min.
6.	100% ETOH	3 min.
7.	90% ETOH	3 min.
8.	80% ETOH	3 min.
9.	70% ETOH	3 min.
10.	50% ETOH	3 min.
11.	Distilled water	4 min.
12.	Cresyl Violet	30 sec.-2 min. (depending upon age of stain)
13.	Distilled water	Rinse
14.	70% ETOH	Differentiate grey matter
15.	90% ETOH	Clear white matter
16.	100% ETOH	Rinse
17.	100% ETOH	5 min.
18.	Xylenes	5 min.
19.	Xylenes	5 min.
20.	Coverslip (Permount)	

*protocol for 50-80 um frozen sections
**Ethyl alcohol in distilled water