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THE MORPHOLOGICAL EFFECTS OF INFANT- AND ADULT-ONSET MONOCULAR PARALYSIS ON CELLS IN THE CAT LATERAL GENICULATE NUCLEUS

The University of North Carolina at Greensboro PH.D. 1984

THE MORPHOLOGICAL EFFECTS OF INFANT- AND ADULT-ONSET MONOCULAR PARALYSIS ON CELLS IN THE CAT LATERAL GENICULATE NUCLEUS

by

Preston Evans Garraghty

A Dissertation Submitted to
the Faculty of the Graduate School at
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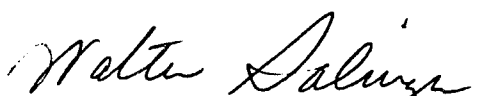

Dissertation Adviser

APPROVAL PAGE

This dissertation has been approved by the following committee of the Faculty of the Graduate School at the University of North Carolina at Greensboro.

Dissertation Adviser Walter L. Salinger

Committee Members P. Scott Lawrence
M. Russell Harter
K. Reed Hunt
Robert E Hatten Jr.

Dec 16 1983
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This experiment has investigated the morphological effects of infant- and adult-onset monocular paralysis on cells in the cat lateral geniculate nucleus (LGN). For comparison, normal adult cats were also studied. These conditions permitted an assessment of the importance of age of onset in the response of the LGN to monocular paralysis.

In the cats monocularly paralyzed as adults, cells were found to be smaller throughout much of the binocular segment of the laminae innervated by the paralyzed eye. This pattern of results was comparable to that seen after infant-onset monocular visual deprivation. The effects of rearing cats with monocular deprivation, however, had been attributed to a putatively developmental mechanism. To the extent that the pattern of effects defines the causal mechanism, one must conclude that the mechanism posited to account for the consequences of infant-onset monocular deprivation is not simply a developmental process.

In the cats reared with monocular paralysis, cells were found to be significantly smaller than normal throughout the binocular segments of the A and A1 laminae in both hemispheres. That is, cells were affected

whether innervated by the paralyzed or mobile eye. This pattern of effects differed markedly from that reported for other infant-onset asymmetric visual deprivations (e.g., monocular deprivation). This difference suggested that the competitive imbalances associated with monocular deprivation might be absent in the monocularly paralyzed cats. Rather, the effects of infant-onset monocular paralysis seemed more consistent with a pattern of competition in which both eyes were equivalently disadvantaged.

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CHAPTER I

INTRODUCTION

A major and enduring issue in psychology involves the question of the relative contributions of nature and nurture to the elaboration of an organism's responsiveness to environmental stimuli. At the physiological level, this issue involves the degree to which the nervous system can be viewed as "hard-wired" and, therefore, impervious to modifications as a function of experience. Obvious avenues for approaching this problem experimentally consist of introducing modifications in the stimulation impinging upon the organism and searching for correlated changes in nervous system structure and/or function. Direct modification of sensory inputs has been perhaps the most widely studied of these avenues.

Classification of Neurons in the Visual System

The classification of neurons is a fundamental step in understanding their function. In the absence of classification only individuals exist, and scientific study is not possible (Pratt, 1972). The problems confronting scientists wishing to classify neurons are comparable to those faced by animal or plant taxonomists in classifying organisms (Tyner, 1975). In all cases, the parameters which contribute to the taxonomy must be identified.

Retina. Hartline (1938) was the first to describe receptive fields of individual retinal ganglion cells in the vertebrate retina. Among other things, he noted that each ganglion cell was connected to only a small region of retina. That is, each had a receptive field. Kuffler (1953) subsequently extended this observation when he reported that the receptive fields of retinal ganglion cells were concentrically organized. These fields were shown to consist of a roughly circular central region and an annular surround with antagonistic stimulus requirements. If the activity of a ganglion cell increased when light fell only on the center of its receptive field, its activity decreased when an annulus of light fell only on its surround (i.e., on-center and off-surround). Other ganglion cells had the complementary receptive field organization (i.e., off-center and on-surround). The existence of these two types of receptive fields permitted the first division of retinal ganglion cells into two nonoverlapping groups based on the organization of their receptive fields.

Later, Enroth-Cugell and Robson (1966) described a different dichotomy of cat retinal ganglion cells and coined the nondescriptive labels Y- and X-cell, each of which included both on- and off-center receptive field types. X- and Y-cells were shown to differ in their response to drifting sinusoidal grating stimuli, receptive field center size, retinal distribution, and the manner in which stimulation of their receptive fields is summed (i.e., linearly or nonlinearly).

Subsequently, a third class of retinal ganglion cells (i.e., W-cells) were reported which differed from both X- and Y-cells (Rodieck, 1967; Rodieck & Stone, 1965; Stone & Fabian, 1966).

Lateral geniculate nucleus. The lateral geniculate nucleus of the cat is a laminated structure which is comprised of no less than six layers. These layers are stacked in retinotopic registry so that a line perpendicular to the dorsal surface represents the same region of visual space viewed through the two eyes (Bishop, Kozak, Levick, & Vakkur, 1962; Kaas, Guillery, & Allman, 1972; Sanderson, 1971b). Two different schemes exist for labeling the layers (Famiglietti, 1975; Guillery, 1970; Hickey & Guillery, 1974; Rioch, 1929; Rodieck, 1979), but they share in common the labels A and A1 for the two most dorsal layers. Laminae A and A1 form a reasonably well matched pair (Kaas, et al., 1972; Sherman & Spear, 1982) and are innervated by the contralateral and ipsilateral eyes, respectively (Garey & Powell, 1968; Guillery, 1966; Hayhow, 1958; Kaas, et al., 1972; Laties & Sprague, 1966; Stone & Hansen, 1966).

Cells in the lateral geniculate nucleus (LGN) of the thalamus constitute the first relay of inputs conveyed by retinal ganglion cell inputs. These cells can also be divided into X-, Y-, and W-cells using essentially the same criteria used at the level of the retina (Bullier & Norton, 1976, 1979a, 1979b; Cleland, Dubin, & Levick, 1971; Cleland, Levick, Morstyn, & Wagner, 1976; Dreher & Sefton, 1979; Friedlander,

Lin, & Sherman, 1979; Friedlander, Lin, Stanford, & Sherman, 1981; Fukada & Saito, 1972; Fukuda & Stone, 1974; Hoffmann, Stone, & Sherman, 1972; Kratz, Webb, & Sherman, 1978b; Lennie, 1980; Rodieck, 1979; Sherman, 1979; Spear, 1984; Stone, Dreher, & Leventhal, 1979; Wilson, Rowe, & Stone, 1976).

Of particular interest for the present purposes is latency of LGN cell response to optic chiasm stimulation (OX latency). OX latency is a derivative of the conduction velocity of retinal ganglion cell axons and the synaptic delay between ganglion cell afferents and their target relay cells. The correspondence between this measure and the other classification criteria generally exceeds 95% (Eysel, Grusser, & Hoffmann, 1979; Garraghty, Salinger, MacAvoy, Schroeder, & Guido, 1982) when W-cells can be excluded. Such an exclusion is easily accomplished in analyzing data from the LGN by considering only cells in laminae A and A1, since W-cells are confined to the four ventral laminae (Sur & Sherman, 1982; Wilson, et al., 1976; Wilson & Stone, 1975). Since little is known about the response of W-cells to sensory modifications, the four ventral layers will not be considered further.

Visual cortex. Several schema, and many parameters exist for the classification of visual cortical neurons. For the present purposes, however, only ocular dominance is of importance. Unlike cells in the retina and LGN, most neurons in visual cortex possess two excitatory receptive fields, one for each eye. Consequently, these cells can be

activated by binocular stimulation, or monocular stimulation through either eye (Bishop, 1973; Hubel & Wiesel, 1959, 1962, 1977). Not all binocular cells, however, are equally responsive to inputs from the two eyes. Rather, varying degrees of ocular dominance are exhibited by different cells, ranging from equal responsiveness to inputs from either eye to exclusive monocularity (Hubel & Wiesel, 1959, 1962, 1977). Further, cells in visual cortex with similar degrees of binocularity are arrayed into ocular dominance columns which extend perpendicularly through cortex (Hubel & Wiesel, 1962, 1977). Within a column, cells have the same (or very similar) degree of binocularity, and ocular dominance shifts systematically from column to adjacent column (Hubel & Wiesel, 1962, 1977). Finally, this high degree of binocular interaction apparently depends upon congruent visual input during the first few postnatal months (Wiesel & Hubel, 1963a, 1963b).

Monocular Deprivation and Neural Plasticity

Since the pioneering work of Nobel laureates David Hubel and Torsten Wiesel first demonstrated changes in the response properties of visual cortical neurons after infant-onset monocular or binocular visual deprivation (Hubel & Wiesel, 1970; Wiesel & Hubel, 1963b, 1965a), the capacity of the developing visual cortex to change its function in the face of alterations in visual inputs has become universally accepted (e.g., see Blake, 1979; Movshon & Van Sluyters, 1979; and Sherman &

Spear, 1982 for recent reviews). A large number of subsequent studies have demonstrated that infant-onset visual deprivation alters the function and structure of subcortical neurons in the lateral geniculate nucleus (Chow & Stewart, 1972; Eysel, et al., 1979; Friedlander, Stanford, & Sherman, 1982; Garey & Blakemore, 1977; Garraghty, Salinger, & Hickey, 1983; Geisert, Spear, Zetlan, & Langsetmo, 1982; Guillery, 1972, 1973; Guillery & Stelzner, 1970; Hamasaki, Rackensperger, & Vesper, 1972; Hickey, 1980; Hickey, Spear, & Kratz, 1977; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Hoffmann & Sireteanu, 1977; Kalil, 1980; Lehmkuhle, Kratz, Mangel, & Sherman, 1980; LeVay & Ferster, 1977; Lin & Sherman, 1978; Maffei & Fiorentini, 1976b; Mangel, Wilson, & Sherman, 1983; Mitzdorf & Neumann, 1978; Sherman, Hoffmann, & Stone, 1972; Sherman, Wilson, & Guillery, 1975; Sireteanu & Hoffmann, 1979; Winfield, Headon, & Powell, 1976; Winfield, Hiorns, & Powell, 1980; Winfield & Powell, 1980), superior colliculus (Berman & Sterling, 1976; Flandrin & Jeannerod, 1977; Hoffmann & Sherman, 1974, 1975; Wickelgren & Sterling, 1969), medial interlaminar nucleus (Kratz, Webb, & Sherman, 1978a), and the nucleus of the optic tract (Hoffmann, 1979).

An important question suggested by the results of experiments investigating the brain's response to sensory modifications regards the precise nature of the response. For example, do changes in the brain after infant-onset monocular deprivation result from active

physiological mechanisms which respond to alterations of inputs in a presumably adaptive fashion, or do such changes merely reflect a passive tropistic reaction?

In the lateral geniculate nucleus, the physiological effects of monocular deprivation can be characterized as a selective reduction in the activity of Y-cells in the laminae innervated by the deprived eye (Geisert, et al., 1982; Sherman, et al., 1972; Sherman & Spear, 1982). Some have suggested that the reduced encounter rate for Y-cells in the deprived LGN laminae of monocularly deprived cats could be due to electrode sampling biases (Eysel, et al., 1979; Shapley & So, 1980; Sherman, et al., 1972; but see Friedlander, et al., 1982). That is, since the average cell size in the deprived laminae of monocularly deprived cats is reduced (Friedlander, et al., 1982; Garey & Blakemore, 1977; Garraghty, et al., 1983; Guillery, 1972, 1973; Guillery & Stelzner, 1970; Hickey, 1980; Hickey, et al., 1977; Hoffmann & Hollander, 1978; Kalil, 1980; Levay & Ferster, 1977; Wiesel & Hubel, 1963a), perhaps the "loss" of Y-cells is an artifact of electrode sampling bias in favor of larger cells (Stone, 1973). If this were the case, then Y-cells in the deprived laminae of monocularly deprived cats might be functionally active, but escape electrophysiological detection merely because of their decreased size. That this is probably not the case has been shown in several ways. First, LeVay and Ferster (1977) have shown that even though the growth of Y-cells in deprived geniculate

laminae is retarded more than that of deprived X-cells, the deprived Y-cell somata are nevertheless still larger than the deprived X-cell somata. Further, a dissociation between average cell size and recorded Y-cell proportions has been shown in several ways. In binocularly sutured cats and cats reared in total darkness, the effects on LGN morphology are relatively slight (Guillery, 1973; Hickey, et al., 1977; Kalil, 1978a; Kratz, Sherman, & Kalil, 1979) in comparison to the physiological loss of recordable Y-cells (Kratz, et al., 1979; Sherman, et al., 1972; Sherman & Spear, 1982). Further, Geisert, et al. (1982) found that cell size was restored to normal in the deprived LGN laminae of monocularly deprived cats by simply enucleating the nondeprived eye, but Y-cell recordability increased only if the deprived eye was also opened. It would appear, therefore, that electrode sampling biases alone cannot account for the reduced encounter rate for deprived Y-cells.

Alternatively, since it is known that the development of Y-cells in the LGN lags behind that of X-cells (Daniels, Pettigrew, & Norman, 1978; Norman, Pettigrew, & Daniels, 1977), it seems possible that the absence of patterned visual stimulation might prevent the normal development of Y-cells. If such were the case, the affected Y-cells could be permanently retarded or simply arrested. That the development of Y-cells has not simply been arrested can be shown readily by merely opening the deprived eye for a period of time. In such animals, the

effects of deprivation in the LGN are still evident (Hoffmann & Cynader, 1977; Wiesel & Hubel, 1965b). In fact, the suppression of inputs from the nondeprived eye is actually increased under conditions of binocular exposure (Glass, 1980; Tumosa, Nunberg, Hirsch, & Tieman, 1983).

Evidence that the effects of monocular deprivation do involve active physiological processes has been suggested by several research strategies. While simply opening the deprived eye does not restore Y-cell function, other experimenters have combined opening the deprived eye with suturing or enucleation of the nondeprived eye. With such paradigms, the effects of monocular deprivation in the LGN were reversed (Geisert, et al., 1982; Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Hoffmann & Sireteanu, 1977; Spear & Hickey, 1979). It would seem, therefore, that the lost Y-cells are being actively suppressed, presumably by a tonically inhibitory mechanism driven by afferent inputs of the nondeprived eye (Movshon & Van Sluyters, 1981).

In visual cortex, the most strikingly evident consequence of monocular deprivation is a shift in binocularity such that the vast majority of cells, which are normally binocular, are driven solely by inputs from the nondeprived eye (Hoffmann & Cynader, 1977; Hubel, Wiesel, & LeVay, 1977; Kratz, Spear, & Smith, 1976; Shatz & Stryker, 1978; Singer, 1977; Smith, Spear, & Kratz, 1978; Spear, Langsetmo, & Smith, 1980; Wiesel & Hubel, 1963b, 1965a; Wilson & Sherman, 1977). This loss of responsiveness to deprived eye inputs apparently does not

result simply from an atrophy of neurons connected to the deprived eye since recordings in monocularly deprived cats reveal no expanses of cortex devoid of neurons responsive to visual activation (e.g., see Movshon & Van Sluyters, 1981). The enucleation reversal paradigm used in assessing Y-cell recovery in the LGN after monocular deprivation has also been used in studying visual cortex (Crewther, Crewther, & Pettigrew, 1977; Hoffmann & Cynader, 1977; Kratz, et al., 1976; Van Sluyters, 1978). Following enucleation of the nondeprived eye and opening of the deprived eye, many more cortical cells are found to be responsive to inputs from the deprived eye. The return of such activity clearly suggests that structural afferents from the deprived eye to cortex remained present throughout the course of deprivation but were not functional, possibly because they were masked by inputs from the nondeprived eye (Blakemore, Hawken, & Mark, 1982; Freeman & Ohzawa, 1983). Such "silent synapses" have been demonstrated to exist in other contexts (e.g., see Merzenich, Kaas, Wall, Nelson, Sur, & Felleman, 1983; Wall & Merrill, 1972).

Somewhat more definitive demonstrations of the active physiological nature of the cortical response to monocular deprivation have been provided by adopting pharmacological approaches. Bicuculline, which blocks the action of the putative inhibitory neurotransmitter gamma-amino-butyric acid (GABA) administered intravenously has been shown to reverse the effects of monocular deprivation just as

effectively as enucleation of the nondeprived eye (Burchfiel & Duffy, 1981; Duffy, Snodgrass, Burchfiel, & Conway, 1976; Sillito, Kemp, & Blakemore, 1981). The tonic inhibitory network involved in the suppression of inputs from the deprived eye, therefore, seemingly relies on intracortical interneurons which use GABA as their transmitter. More general statements about neural plasticity have made based on a series of experiments assessing the importance of the noradrenergic system (e.g., see Moore & Bloom, 1979) in mediating the cortical response to monocular deprivation (Kasamatsu & Pettigrew, 1976, 1979; Kasamatsu, Pettigrew, & Ary, 1979; Pettigrew & Kasamatsu, 1978). In their initial experiments (Kasamatsu & Pettigrew, 1976, 1979), norepinephrine was depleted from the brains of kittens by administering the catecholaminergic neurotoxin, 6-hydroxydopamine (6-OHDA). The visual cortex of 6-OHDA-treated kittens retained normal binocularity after monocular deprivation. Subsequently, it was shown that intracortical perfusion of norepinephrine in monocularly deprived cats previously treated with 6-OHDA restored the capacity of the visual system to silence inputs from the deprived eye (Kasamatsu, Pettigrew, & Ary, 1979; Pettigrew & Kasamatsu, 1978). The changes in binocularity in cortex which normally follow monocular deprivation must also, therefore, result, at least to some degree, from tonic physiological suppression.

Artificial Strabismus

Misalignment of the two eyes (strabismus) induced by sectioning one or more of the muscles of one eye would seem to alter visual inputs less severely than eyelid suture. Artificial strabismus, however, produces marked changes in the physiology of the visual system. Hubel and Wiesel (1965) first demonstrated that induced strabismus produces a large reduction in the number of binocularly activated neurons in visual cortex, and this finding has been widely replicated (Bennett, Smith, Harwerth, & Crawford, 1980; Blakemore, 1976; Blakemore & Eggers, 1978, 1979; Freeman & Tsumoto, 1983; Gordon & Gummow, 1975; Ikeda & Tremain, 1977; Levitt & Van Sluyters, 1982; Van Sluyters & Levitt, 1980; Wickelgren-Gordon, 1972; Yinon, 1976; Yinon, Auerbach, Blank, & Friesenhausen, 1975). In the lateral geniculate nucleus, the spatial resolving power of cells receiving innervation from the deviating eye is reduced, but no such reduction has been found in cells innervated by the normal eye or in cells innervated by more peripheral retina of the deviating eye (Ikeda & Wright, 1976). Interestingly, these effects were found to be more pronounced in lamina A1 than in lamina A (Ikeda, Plant, & Tremain, 1977).

The consequences of artificial strabismus differ from those of monocular deprivation in at least one important respect. Monocular deprivation reduces cortical binocularity by functionally eliminating the inputs from the deprived eye. The preponderance of cells are then

monocularly driven by the nondeprived eye. Artificial strabismus, on the other hand, reduces binocularity in cortex by increasing the number of monocular units activated by either eye. That is, there is no comparable elimination of squinted eye inputs to cortex (Bennett, et al., 1980; Blakemore & Eggers, 1978, 1979; Chino, Shansky, Jankowski, & Banser, 1983; Kalil, Spear, & Langsetmo, 1978; Yinon, 1976; Yinon, et al., 1975). At the level of the cortex, therefore, the mechanisms responsible for the effects of monocular deprivation and strabismus probably differ. This may also be true in the LGN where the most prominent effects of monocular deprivation involve Y-cells (e.g., Friedlander, et al., 1982; Sherman, et al., 1972; Sherman & Spear, 1982) while X-cells are most affected by strabismus (e.g., Ikeda, et al., 1977; Ikeda & Wright, 1976; Tsumoto & Freeman, 1981). It seems likely, therefore, that the mechanisms affected by monocular deprivation and strabismus probably differ.

Development of the Visual System

Visual acuity. At birth, cats (Barlow, 1975; Freeman & Marg, 1975; Mitchell, Giffen, Wilkinson, Anderson, & Smith, 1976), monkeys (Lee & Boothe, 1981), and humans (Dobson, Mayer, & Lee, 1980) have very poor visual acuity relative to ultimately achieved adult values. Furthermore, the level of acuity present at any age is related not to postnatal age but rather to postconception age (Dobson, et al., 1980;

Lee & Boothe, 1981), suggesting that the development of visual acuity is genetically controlled. Normal visual experience is required, however, in order for acuity to develop to adult levels. If, for example, cats are reared in the dark, they are functionally blind when brought into the light (Timney, Mitchell, & Giffen, 1978). In cats reared in a normal visual environment, acuity develops to adult values by the end of the third postnatal month (Barlow, 1975; Freeman & Marg, 1975; Mitchell, et al., 1976).

Lateral geniculate nucleus. At birth, cells in the LGN are immature. Daniels, et al. (1978) found geniculate cells had abnormally large receptive fields, weak or absent antagonistic surrounds, and reduced responsiveness and sensitivity to light. As would be expected, cells in the infant LGN are also much smaller than they are in adults (Hickey, 1980; Kalil, 1978b, 1980). Given normal postnatal visual experience, these properties acquire adult-like characteristics by the time the cat is three to four months of age (Hickey, 1980; Kalil, 1978b, 1980; Mangel, et al., 1983). Moreover, the growth of cells in the LGN proceeds in the absence of visual exposure. Dark-reared cats and monkeys have geniculate cells that are normal in size (Hendrickson & Boothe, 1976; Kratz, et al., 1979). Further, it appears that the spatial resolving power of LGN X-cells continues to improve into the third month of life (Ikeda & Tremain, 1978b), but, again, only with normal experience (Hoffmann & Sireteanu, 1977; Lehmkuhle, Kratz,

Mangel, & Sherman, 1978, 1980; Lehmkuhle, Kratz, & Sherman, 1982; Mangel, et al., 1983; Mower & Christen, 1982).

Visual cortex. At the time of natural eye opening in the cat (at about 8 days), only about 10% of the normal adult complement of cortical synapses are present. In normally-reared cats, there is then a burst of synaptogenesis with adult levels reached between the third and fourth postnatal month (Cragg, 1972). If normal visual exposure is not permitted, however, many fewer synapses are found in cortex (Cragg, 1975). Hubel and Wiesel (1963) found that inexperienced cells in kitten visual cortex were weak and erratic in their responsiveness. Binocularity, however, was present in the naive cortex. While physiological recording in the immature cortex of monkeys and kittens (Blakemore, 1977; Blakemore, Van Sluyters, & Movshon, 1975; Wiesel & Hubel, 1974) show evidence of the normal periodic variation in eye dominance seen in adults (Hubel & Wiesel, 1965; Shatz, Lindstrom, & Wiesel, 1977; Shatz & Stryker, 1978), anatomically demonstrable segregation (e.g., by injecting anatomical tracers in one eye) becomes considerably more pronounced during the first postnatal months (Hubel, et al., 1977; LeVay, Stryker, & Shatz, 1978; Rakic, 1977). Further, binocularity is retained in the cortex of dark-reared cats (Cynader, Berman, & Hein, 1976; Imbert & Busseret, 1975; Mower, Berry, Burchfiel, & Duffy, 1981). While these data taken together suggest that binocularity is present in the inexperienced kitten cortex, normal

binocular experience is required for the refinement of the binocular receptive fields necessary for disparity sensitivity (Blakemore & Van Sluyters, 1975; Pettigrew, 1974). That is, patterned visual experience presented to the two eyes alternately will generally promote the development of normal levels of visual acuity, but the development of stereopsis requires simultaneous binocular experience (Barlow & Pettigrew, 1971; Blakemore & Van Sluyters, 1975; Movshon, 1976; Pettigrew, 1974). These data are comparable to human clinical observations which show that patching the normal eye of strabismic children, and, therefore, enforced usage of the deviated eye can promote normal visual acuity in the squinted eye (Vaughan & Asbury, 1980). Stereoscopic vision, on the other hand, only very rarely develops in these individuals (Vaughan & Asbury, 1980).

The reversals of the physiological effects of monocular deprivation in the visual cortex using reverse suture with enucleation of the nondeprived eye (e.g., Kratz, et al., 1976), the application of bicuculline (e.g., Sillito, et al., 1981), or perfusion with norepinephrine (e.g., Kasamatsu, et al., 1979) have all been incomplete. For example, in the cortex of monocularly deprived cats, only about 5% of the cells will respond to inputs through the deprived eye as compared to about 80% in normal cats (e.g., Kratz, et al., 1976). When the nondeprived is enucleated, however, inputs from the deprived eye can drive no fewer than 30% of the cortical cells (Crewther, et al., 1978;

Hoffmann & Cynader, 1977; Kratz, et al., 1976; Smith, et al., 1978; Spear, 1978). This failure to recover completely is not surprising in light of the profound structural changes which accompany visual deprivation (Cragg, 1975; Stryker & Shatz, 1976; Sur, Humphrey, & Sherman, 1982; Thorpe & Blakemore, 1975). In any event, it appears that ineffective synapses (Wall & Merrill, 1972) may have been unmasked permitting deprived eye inputs to drive cortical cells. Indeed, subthreshold inputs from the deprived eye can be recorded in cortex under appropriate conditions (Blakemore, et al., 1982). Further, even though the deprived eye can drive many more cortical cells under these circumstances, the response characteristics normally found in mature cortical cells (e.g., orientation selectivity) are absent (Spear, et al., 1980). Finally, these properties fail to develop in such animals suggesting that not only is experience required for their development, but that the experience must occur during development.

The data reviewed briefly above suggest that the balance of postnatal visual development in the cat is completed by the time the animal is four months of age. A similar conclusion can be derived from studies which have either assesssed the effects of a sensory perturbation as a function of age (i.e., delayed the onset of the insult), or attempted to reverse the effects of an insult within the critical period (see Movshon & Van Sluyters, 1981; Sherman & Spear, 1982 for reviews). Infant-onset visual deprivation, strabismus, or

anisometropia have all been shown to have profound effects on visual acuity (e.g., Lehmkuhle, et al., 1982), LGN physiology (e.g., Geisert, et al., 1982) and morphology (e.g., Hickey, ey al., 1977), and cortical physiology (e.g., Wiesel & Hubel, 1963b) and morphology (e.g., Cragg, 1975). Studies which have assessed these effects while varying the age of onset and/or the duration of the visual insult have arrived at similar conclusions regarding the temporal extent of the so-called critical period (Olson & Freeman, 1980; and see Movshon & Van Sluyters, 1981 for a review). These observations have also shown that some aspects of visual system structure and function develop normally even in the complete absence of postnatal visual experience (e.g., cell size in dark-reared cats), while other, such as the development of eye alignment, require normal binocular experience.

Monocular Paralysis in the Adult Cat

Several recent experiments have demonstrated that changes in the function of visual cortical neurons are observable after adult-onset stimulus perturbations (Buchtel, Berlucchi, & Mascetti, 1975; Fiorentini & Maffei, 1974; Fiorentini, Maffei, & Bisti, 1979; Maffei & Fiorentini, 1976a; but see Berman, Murphy, & Salinger, 1979). Further, Salinger and colleagues have shown that neurons in the lateral geniculate nucleus (LGN) have altered structure and function after adult-onset visual sensory modifications (Brown & Salinger, 1975;

Garraghty, et al., 1982; Guido, Salinger, & Schroeder, 1982; MacAvoy & Salinger, 1980; Salinger, 1977; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, Garraghty, & Schwartz, 1980; Salinger, Schwartz, & Wilkerson, 1977a, 1977b; Salinger, Wilkerson, & MacAvoy, 1977; Schroeder & Salinger, 1978; Wilkerson, Salinger, & MacAvoy, 1977). As with cortical neurons, therefore, subcortical neurons are also responsive to alterations in sensory inputs, and this sensitivity is not restricted to a critical period early in development (see Carlin & Siekevitz, 1983; Dietrich, Durham, Lowry, & Woolsey, 1981; Franck, 1980; Lund, 1978; Merrill & Wall, 1978; Merzenich, et al., 1983; Robbins, 1980; Wong-Riley, Merzenich, & Leake, 1978; Wong-Riley & Welt, 1980 for examples of neural plasticity in other systems and structures).

The experimental paradigm adopted by Salinger and colleagues involves the unilateral transection of cranial oculomotor nerves III, IV, and VI which innervate the intrinsic and extrinsic muscles of the eye. With their transection, the operated eye is rendered incapable of movement in its orbit and unable to accommodate. The change in the physiology of cells in the LGN observed after monocular paralysis has been characterized as a shift in the relative electrophysiological encounter rate for X- and Y-cells (Brown & Salinger, 1975; Garraghty, et al., 1982; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, et al., 1977b). Using OX latency as a means of cell type

identification, monocular paralysis results in a decrease in the encounter rate for X-cells, and a complementary increase in the encounter rate for Y-cells. That is, while the average number of cells recorded during a given electrode penetration does not change, relative to normal, the proportions of recorded X- and Y-cells are altered (Garraghty, et al., 1982). Therefore, if the OX latencies of cells recorded in the LGN are pooled to form relative frequency distributions, the OX latency distribution after two weeks of monocular paralysis (chronic monocular paralysis: CHMP) shows a decrease in encounter rate for long latency (X) cells and an increase for shorter latency (Y) cells, relative to normal.

Monocular Paralysis in the Infant

Relatively little work has been done with cats reared with monocular paralysis. Salinger, MacAvoy, and Garraghty (1978) reported that the effects of infant-onset monocular paralysis differed from those found in animals paralyzed as adults. The OX latency distributions of LGN cells recorded in these animals suggested that both X- and Y-cells were lost. Salinger, et al. (1978) hypothesized that the Y-cell loss occurred during maturation, as with infant-onset monocular deprivation, with an additional loss of X-cells superimposed during adulthood. This aspect of the effect of infant-onset monocular paralysis is logically consistent with recent behavioral data from animals reared with induced

squint (Holopigian & Blake, 1983) which suggested that both X- and Y-cells were affected by the strabismus. Furthermore, in the monocularly paralyzed infants, the physiological effects were found in both laminae A and A1 in the LGN contralateral to the paralyzed eye (i.e., whether the innervating eye was paralyzed or mobile). This result may be consistent with cortical recording data in strabismic kittens (Chino, et al., 1983) which showed aberrant responsiveness on the part of cortical cells even when stimulated through the "normal" eye. The observations in the monocularly paralyzed kittens are not, however, in agreement with the geniculate recordings of Ikeda and colleagues (Ikeda, et al., 1977; Ikeda & Tremain, 1979; Ikeda & Wright, 1976) who have suggested that the physiological effects of artificial squint are confined to the LGN laminae innervated by the deviated eye. This difference is difficult to resolve since their work may also be at variance with the recent observations of Chino, et al. (1983) and Holopigian and Blake (1983).

Are the Effects of Monocular Paralysis Due to an Active Physiological Process?

The decline in the encounter rate for X-cells in the LGN after monocular paralysis was one of the first demonstrations of neural plasticity in an adult mammal (Brown & Salinger, 1975). These data, however, cannot in principle provide information regarding the nature of

the mechanism responsible for the changes in LGN physiology. Such changes could result from some unspecified degenerative process secondary to cranial nerve atrophy accompanying transection, or the silencing of X-cells could be due to tonic physiological inhibition. Salinger, et al. (1977b) initially posited an active physiological mechanism because X-cells were lost not only in the layers of the LGN innervated by the paralyzed eye, but also in those laminae innervated by the mobile eye. While a passive process might account for the changes in the layers receiving inputs from the operated eye, more active processes, displaying sensitivity to binocular disruptions, would presumably be required to explain the effects in the laminae innervated by the unoperated eye.

Other data are available to support this tentative conclusion. For example, monocular paralysis consists of a complex of stimulus distortions: paralysis of the intrinsic eye muscles results in a loss of accommodative and pupillary control mechanisms, while unilateral paralysis of the extrinsic eye muscles produces a misalignment of the visual axes of the two eyes, and consequently, abnormal patterns of retinal disparity and oculomotricity. Since independent paralysis of either set of these muscles can produce amblyopia (Vaughan & Asbury, 1980), clinically useful information can potentially be gathered by isolating paralysis of the separate sets of muscles and assessing their contributions to the effects of monocular paralysis. In doing so, it

was shown that intrinsic muscular paralysis accomplished with topical applications of the cycloplegic atropine had no effect, while tenotomization of the extrinsic eye muscles produced effects in the LGN which were of the same magnitude as those resulting from combined paralysis of both muscle sets using cranial nerve section (Salinger, Garraghty, MacAvoy, & Hooker, 1980). Since comparable effects are produced by both monocular paralysis and monocular tenotomy, and they seemingly share no surgical risks or opportunities for degenerative processes, these data provided additional indirect support for the hypothesis that the effects of monocular paralysis stem from the inhibitory consequences of an active physiological mechanism.

As was the case with researchers investigating monocular deprivation, more direct support for an active process operating in monocularly paralyzed cats has been derived from protection and reversal research strategies. Protection from the effects of monocular paralysis was first demonstrated using concurrent bilateral eyelid suture (Salinger, Garraghty, & Schwartz, 1980; Schwartz, Salinger, & Wilkerson, 1976). When patterned vision was denied during the course of monocular paralysis, its effects were partially blocked. A degenerative process initiated by either cranial nerve transection or extraocular muscle tenotomy would presumably be unaffected by the presence or absence of patterned visual inputs. Protection from the usual consequences of monocular paralysis has also been demonstrated

pharmacologically (Guido, et al., 1982). When 6-OHDA was administered intraventricularly in conjunction with monocular paralysis, no changes in the physiology of the LGN were observed. That monocular paralysis was without effect when a family of neurotransmitters were selectively eliminated clearly lends credence to the hypothesis that an active physiological mechanism is responsible for the loss of X-cells generally found.

Additional support for this hypothesis has been derived from three reversal paradigms. The first involved sequential paralysis of both eyes. The effects of monocular paralysis require two weeks to become manifest. If both eyes are paralyzed at the same time, however, immediate changes in the physiology of LGN X-cells are observable (Salinger, Wilkerson, & MacAvoy, 1977; Wilkerson, et al., 1977). Further, the effects of binocular paralysis, while occurring more swiftly, were less profound than those of CHMP. Using this information, Schroeder and Salinger (1978) followed two weeks of monocular paralysis with surgical paralysis of the second eye. They found that the effects of monocular paralysis, which were presumably present after the initial two week period, were reduced by the paralysis of the second eye.

A second reversal manipulation involved the use of consecutive bilateral eyelid suture. As stated previously, it had been shown that the elimination of patterned visual inputs during the course of CHMP protected the LGN X-cells to a certain degree (Salinger, Garraghty, &

Schwartz, 1980; Schwartz, et al., 1976). Could it be the case then that following chronic monocular paralysis with a period of patterned visual deprivation would reverse the initial effects to a comparable degree. Again, since the effects of CHMP were presumably present after the initial two week period, any mitigation by the subsequent lid suture would reflect a reversal. The results of this experiment did demonstrate a partial reversal (Salinger, 1977). The partial reversals achieved by these two experimental manipulations demonstrated that at least a portion of the CHMP effect stemmed from physiological suppression. However, since nerve transection itself is irreversible, it seemed that a complete reversal might be impossible to accomplish, and in the absence of such an observation the characterization of the CHMP effect as active and physiological remained tentative.

A more dramatic demonstration that in fact all of the X-cell loss after CHMP is attributable to the activity of a physiological mechanism involved varying the level of anesthesia of subjects during recording (Garraghty, et al., 1982). The initial reports of Salinger and colleagues (Brown & Salinger, 1975; Salinger, et al., 1977b; Salinger, Garraghty, MacAvoy, & Hooker, 1980) on the effects of chronic monocular paralysis involved subjects which were merely sedated during physiological recording. A systematic assessment of the effects of anesthetic level on the recordability of X-cells after CHMP, however, showed that high levels of anesthesia completely eliminate the effects

of CHMP (i.e., normal proportions of X- and Y-cells were recorded), and this effect of anesthesia was evident immediately (Garraghty, et al., 1982). Unfortunately sodium pentobarbital has broad pharmacological effects, so the identification of the site of action of the anesthetic could be merely speculative. In any event, the reversal of the effects of CHMP by pharmacological manipulation clearly implies that the effects did not arise dué to some passive degenerative process.

Similar conclusions cannot, unfortunately, be reached for cats reared with monocular paralysis because reversal and/or protection experiments have not been performed in such subjects. This, together with the apparently different physiological consequences of infant- and adult-onset monocular paralysis, does not permit the conclusions drawn from the adult data to be generalized to the subjects reared with monocular paralysis. Further, it is certainly not clear that the consequences of infant- and adult-onset monocular paralysis depend upon common mechanisms.

Correspondence Between Physiology and Morphology

The consistency of the physiological effects observed in the LGN after CHMP (Brown & Salinger, 1975; Garraghty, et al., 1982; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Salinger, et al., 1977b) prompts speculation regarding possible correlated morphological changes. For example, it has been known for over 70 years that neurons in the LGN

atrophy when inputs from the retina are interrupted (Cowan, 1970). Further, complete interruption of retinal afferents is not necessary for atrophy to be observed in the LGN. Numerous reports in the literature have shown that the sizes of LGN cells are affected by infant-onset monocular deprivation in cats (Friedlander, et al., 1982; Garey & Blakemore, 1977; Garraghty, et al., 1983; Guillery, 1972, 1973; Guillery & Stelzner, 1970; Hickey, 1980; Hickey, et al., 1977; Hoffmann & Hollander, 1978; Kalil, 1980; Kupfer & Palmer, 1964; LeVay & Ferster, 1977; Wiesel & Hubel, 1963a). Furthermore, these morphological data have been shown to be highly correlated with the pattern of physiological changes in the LGN after deprivation. That is, after monocular deprivation, physiological Y-cell lossess are severe in the binocular segments of laminae innervated by the deprived eye, but are considerably more modest in the deprived monocular segment (Sherman, et al., 1972; Sherman & Spear, 1982). Similarly, the morphological effects of monocular deprivation are considerably more pronounced in the deprived binocular segments than in the deprived monocular segment (Hickey, 1980; Hickey, et al., 1977; Kalil, 1980). Binocular deprivation, on the other hand, produces physiological Y-cell losses which are less severe than those found in the binocular segment after monocular deprivation, but which are nevertheless found throughout the LGN with no discernible differences in magnitude between monocular and binocular segments (Kratz, et al., 1979; Sherman, et al., 1972).

Correspondingly, cell body size decreases in the LGN are smaller than those found in the binocular segments of monocularly deprived cats, but are of equivalent magnitude in both the binocular and monocular segments. There is, therefore, in monocularly and binocularly deprived cats a good corrrespondence between the pattern of physiological Y-cell loss and the pattern of morphological cell shrinkage.

Very little work of this sort has been conducted in strabismic cats. Ikeda, et al. (1977) reported that cells in the geniculate laminae innervated by the deviated eye were smaller than normal. Further, in close agreement with their physiological data, they found the shrinkage to be most pronounced in regions of the LGN representing central visual space, with more peripherally located geniculate regions being relatively less affected.

It has been shown previously that two weeks of monocular paralysis in the adult cat produces changes in the average cell size of some neurons in the LGN (Garraghty, et al., 1982). In that report, cell body size measurements were made in both hemispheres in the portion of the LGN representing 6-20^{o} of visual space (i.e., measured with respect to the vertical meridian). Physiological recordings in the representation of these eccentricities in the LGN contralateral to the paralyzed eye had demonstrated that fewer X-cells were encountered in lamina A, innervated by the paralyzed eye, while lamina A1, innervated by the mobile eye, was no different from normal (Garraghty, et al., 1982).

While physiological recordings within the representation of these eccentricities were not made in the LGN ipsilateral to the paralyzed eye, recordings in the representation of 0-5° showed that the effects of CHMP were comparable in the two hemispheres (Garraghty, et al., 1982; MacAvoy & Salinger, 1980). Corresponding to the pattern of X-cell loss in the LGN contralateral to the paralyzed eye, the cells in lamina A representing 6-20° of visual space were found to be smaller, on the average, than normal, while cell body size in the A1 lamina representation of 6-20° of visual space appeared normal in size (Garraghty, et al., 1982).

Dissociation Between Physiology and Morphology

While the data presented above demonstrate that cell body size and electrophysiology are often related, there are examples of a dissociation between cell body size and the encounterability of X- and Y-cells. Geisert, et al. (1982) have shown that the cell shrinkage which accompanies infant-onset monocular deprivation is reversed by enucleation of the nondeprived eye even when the initially deprived eye remains closed, but under these circumstances the loss of Y-cells is still evident. If the intially deprived eye is then opened, however, Y-cells recover physiologically. In the reverse sutured cats, therefore, cell size is normal but physiology is not. Similarly, in dark-reared cats, Y-cells are lost physiologically throughout the LGN,

but cells are of normal size (Kalil, 1978a; Kratz, et al., 1979). Normal physiological encounter rates for X- and Y-cells in shrunken geniculate laminae has also been demonstrated in monocularly deprived primates. Average cell size in LGN laminae innervated by the deprived eye is reduced by monocular deprivation in primates (Casagrande & Joseph, 1980; Vital-Durand, Garey, & Blakemore, 1978; Von Noorden & Middleditch, 1975). The encounter rate for X- and Y-cells in these deprived LGN laminae, however, is normal (Irwin, Sesma, Kuyk, Norton, & Casagrande, 1983; Sesma, Kuyk, Norton, & Casagrande, 1982). A different kind of dissociation of physiological encounter rate and cell size has been shown in the nondeprived laminae of monocularly deprived cats. In these layers, average cell size has been found to be larger than normal (Hickey, et al., 1977; Wan & Cragg, 1976). The presence of this hypertrophy, however, has no apparent effect on physiological encounter rates (Sherman, et al., 1972; Sherman & Spear, 1982).

Purposes of the Present Study

Aside from assessing the extent to which LGN physiology can or cannot be used to predict morphology after infant- and adult-onset monocular paralysis, the proposed experiment also offers the opportunity to view monocular paralysis in a developmental context. Salinger, et al. (1978) presented the question in the context of infant-onset visual deprivation and adult-onset monocular paralysis. Infant-onset monocular

deprivation has its principal effect on LGN Y-cells (e.g., Sherman, et al., 1972) while adult-onset monocular paralysis affects X-cells (e.g., Salinger, et al., 1977b). The fact that these two stimulus disruptions impact upon different cell classes could be due to one or more of several factors. First, obviously, the age at time of onset of the insult differs. Since Y-cells do develop later than X-cells (Daniels, et al., 1978; Norman, et al., 1977), this age difference could be the main reason that Y-cells are lost with infant-onset monocular deprivation while X-cells are lost with adult-onset monocular paralysis. Some support for this possibility can be derived from the observations that infant-onset binocular deprivation affects Y-cells (e.g., Sherman, et al., 1972) while adult-onset binocular deprivation affects X-cells (Salinger, et al., 1977a). Secondly, the nature of the stimulus disturbance differs between the two conditions. With monocular deprivation, patterned visual input is denied to one eye. On the other hand, with monocular paralysis, the misalignment of the visual axes causes a disruption in the normal pattern of retinal disparity. Perhaps patterned visual input is necessary for the maintainence of normal Y-cell activity while X-cells require not only patterned input but also normal patterns of retinal disparity and oculomotricity. The differential effects of infant- and adult-onset binocular deprivation mentioned above argue against this position. Support for this possibility, however, exists in the reported differences in the effects

of infant-onset monocular deprivation and artificial strabismus (e.g., Sherman, et al., 1972; Ikeda, et al., 1977). Artificial strabismus, like monocular paralysis, is characterized by a misalignment of the visual axes. Also like adult-onset monocular paralysis, infant-onset strabismus seems to affect principally X-cells (e.g., Ikeda, et al., 1977). Therefore, while infant-onset monocular deprivation and artificial strabismus have effects on both X- and Y-cells (Ikeda & Tremain, 1979; Mangel, et al., 1983), they differ in terms of the class of cells upon which they have the greatest impact. Finally, infant-onset monocular deprivation and adult-onset monocular paralysis differ in duration of insult. In general, cats reared with monocular deprivation are at least six months of age at the time of study. That is, they have experienced at least five months of monocular deprivation. On the other hand, monocularly paralyzed adult cats have generally been studied two weeks after the surgery was performed. Perhaps the longer duration involved in studies of infant-onset monocular deprivation is responsible for the loss of Y-cells usually found in those cats.

Monocular paralysis beginning in infancy or adulthood clearly presents the subject with the same sensory disturbance. Any differences in the responses of the infant and adult visual systems to monocular paralysis, therefore, would seemingly have to be due to the differences in age of onset, since duration and content of stimulus disruption are held constant. To the extent that differences do exist, it may be

possible to suggest reasons for these differences and determine their implications for development.

Infant-onset monocular paralysis and monocular deprivation confront the visual system with qualitatively different sensory disturbances. Since age of onset and duration are controlled, any difference in the effects of these preparations would most likely arise due to the differences between the stimulus disruptions. Different sensitivities of the immature visual system to these conditions would seem to have implications for theories concerning cell size development in the LGN.

The cell size data from cats monocularly paralyzed as adults and infants can also be used to readdress general issues related to cell body size and what this morphological feature reflects. Numerous correlations have been observed between LGN cell size and other aspects of the visual system. The examples of certain dissociations introduced previously, however, raise the possibility that the associations which have been presented in the literature are fortuitous, and do not reflect causal relationships. Data from the monocularly paralyzed infants and adults together with other observations in the literature permit a reassessment of the issue of what changes in LGN cell size reflect.

CHAPTER II

METHODS

Thirteen adult cats were subjects in this experiment. Of these, four were reared with monocular paralysis, four underwent a prolonged period of monocular paralysis as adults, and five were normal controls. These animals weighed no less than 2.0 kg at the time of sacrifice. All cats were permitted free access to food and water, and were housed in an open colony which met all relevant FDA regulations.

The cats which were reared with monocular paralysis were taken from litters born in the animal colony. Monocular paralysis surgery was performed upon these animals when they were between three and four weeks of age. They were then returned to their mothers and, upon weaning, reared in the open animal colony. These cats were at least one year old at the time of sacrifice.

The adult cats which underwent monocular paralysis and the normal control cats were acquired locally. The monocularly paralyzed adult cats were housed in the animal colony for no less than one year after surgery so that duration of monocular paralysis was roughly equal for the infant- and adult-onset cats.

Monocular paralysis. Monocular paralysis was accomplished by transection of cranial motor nerves III, IV, and VI. Prior to the

surgery, subjects were anesthetized with intraperitoneal injections of acepromazine maleate (2.9 mg/kg) and sodium pentobarbital (15.0 mg/kg). The animals were then placed in a specially constructed head holding device which allowed access to the roof of the mouth. Having the roof of the mouth so exposed permitted a ventral approach through the soft palate, nasopharynx, and sphenoid sinus to expose nerves III, IV, VI, and the ophthalmic branch of nerve V just caudal to the orbit. Cranial nerves III, IV, and VI were then severed while care was taken not to damage the ophthalmic branch of nerve V or the adjacent arteries. To avoid damage to the orbit, the optic nerve, and the central nervous system, the bony covering of nerve II, the orbit, and the optic chiasm, and the dural covering of the cerebrum remained intact. This method of ocular paralysis avoids the potential difficulties which could arise from a dorsal approach in which the dura would be breached and large masses of cortical tissue would have to be displaced to give access to the cranial nerve trunks. The cavity created by the surgery was then bathed with penicillin and filled with gel foam, and the incision in the palate was closed with sutures. Following the surgery, the animals were placed on a twice daily regimen of antibiotics (penicillin and tylosin). Throughout the course of the paralysis, eye medication (a mixture of bacitracin, neomycin, and polymyxin with or without hydrocortisone acetate) was used prophylactically as needed. No serious corneal lesions developed in any of the monocularly paralyzed subjects making it

very unlikely that any of the ultimate effects were due to "monocular deprivation."

Brain extraction and preparation for anatomical assessment. In preparation for the collection of anatomical data, all cats were deeply anesthetized with either sodium pentobarbital (50-60 mg/kg) or ketamine hydrochloride (80-100 mg/kg). The animals were then perfused through the heart with 0.9% buffered saline followed by 10% formalin. The brains were then extracted from the cranium and stored in 10% formalin with 30% sucrose by volume. Prior to sectioning, the brains were blocked by cutting off the frontal cortex coronally just rostral of the ansate sulcus. This blocking procedure provided a flat surface for the remaining brain to rest upon for the collection of caudal-to-rostral coronal sections. The flat rostral surface of the brain was then placed on the cutting stage of a freezing microtome and frozen in place with a mixture of dry ice and the solution in which the brain was stored. The blocked brain was positioned with the ventral surface of the cortex facing the blade. A hole was placed in the white matter of either the left or right hemisphere with a syringe needle to eliminate confusion when the sections were mounted. Sections were cut at 60 μm and stored individually in bins of collecting trays. The collecting trays consisted of a 10X8 matrix of bins filled with buffered 10% formalin.

Cell body measurements. The cross-sectional areas of 1400 LGN cells were measured in each subject. Measurements were made in both

hemispheres in portions of the LGNs representing 0-5°, 6-20°, 21-45°, and 46-90°. Figures 1 and 2 show a photomicrograph of a coronal section through the lateral geniculate nucleus and a drawing of the LGN with isoeccentricity lines superimposed (adapted from Kaas, et al., 1972; Sanderson, 1971a, 1971b). As can be seen in Figures 1 and 2, making measurements within the intended eccentricity zones was relatively simple. Measurements in the area representing 0-5° were made in the medial-most portion of the geniculate in which distinct A and A1 laminae are evident. The measurements of cells in the representation of 6-20° were made in the middle of the mediolateral extent of the binocular portion of the LGN. Measurements of cells in the bin representing 21-45° were made toward the lateral-most part of the binocular segment. Monocular segment (i.e., 46-90°) measurements were made in the middle of the monocular segment. All measurements were made at Sanderson's coronal 5 (Sanderson, 1971b) which is the anterior-posterior midpoint of the LGN. This coronal level was determined by halving the distance between the rostral-most and caudal-most brain sections containing parts of the lateral geniculate nucleus. The determination of the anterior and posterior ends of the LGN were made based on brain sections stained for Nissl substance with cresyl violet after having been mounted on glass slides. The protocol for cresyl violet staining is given in Appendix A. The brain sections containing Sanderson's coronal 5 were also stained with cresyl violet in preparation for the collection of

Figure 1. Low power photomicrograph of a coronal section through the cat LGN. Note the distinctness of laminae A and A1 relative to the C complex.

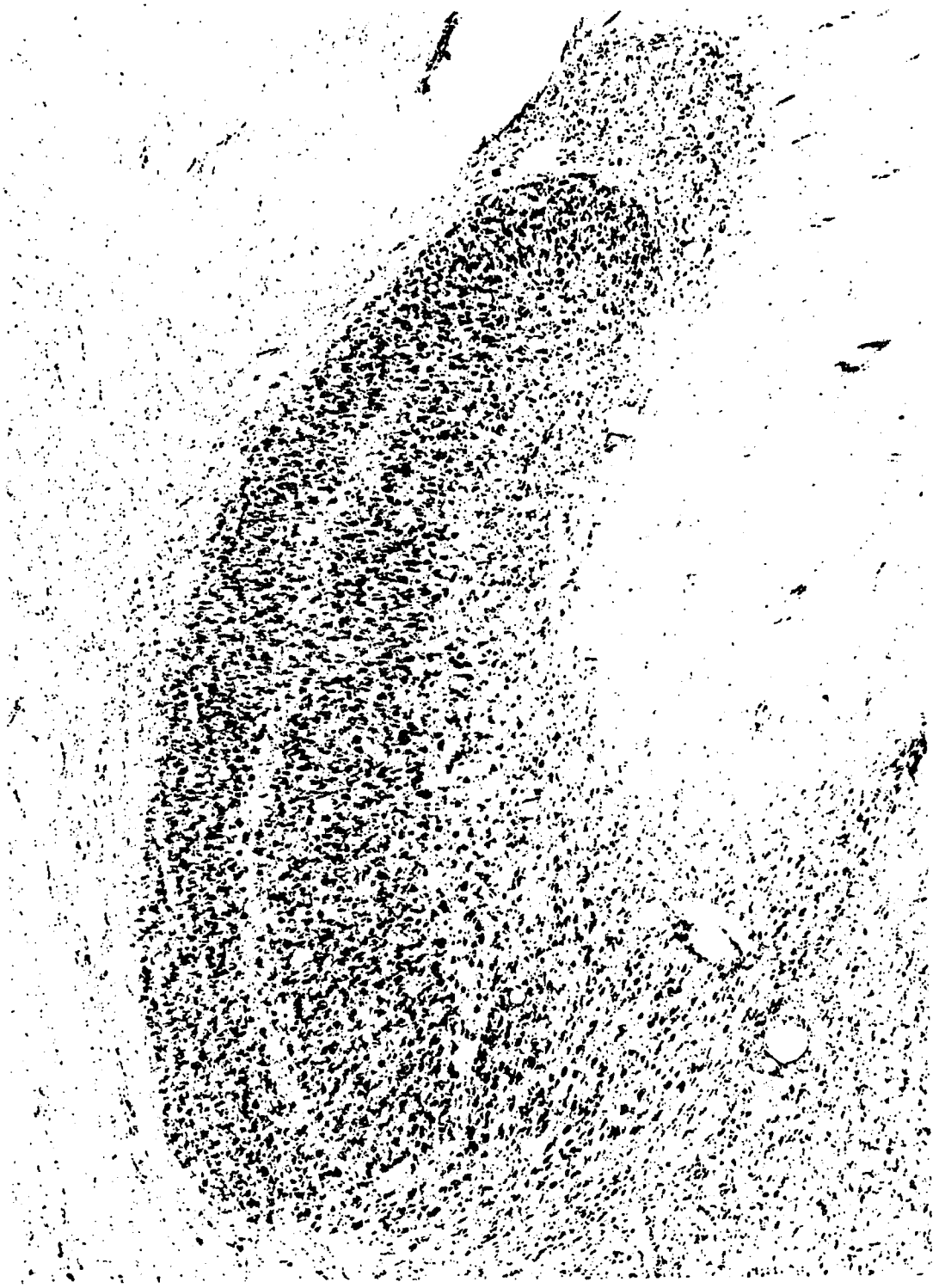
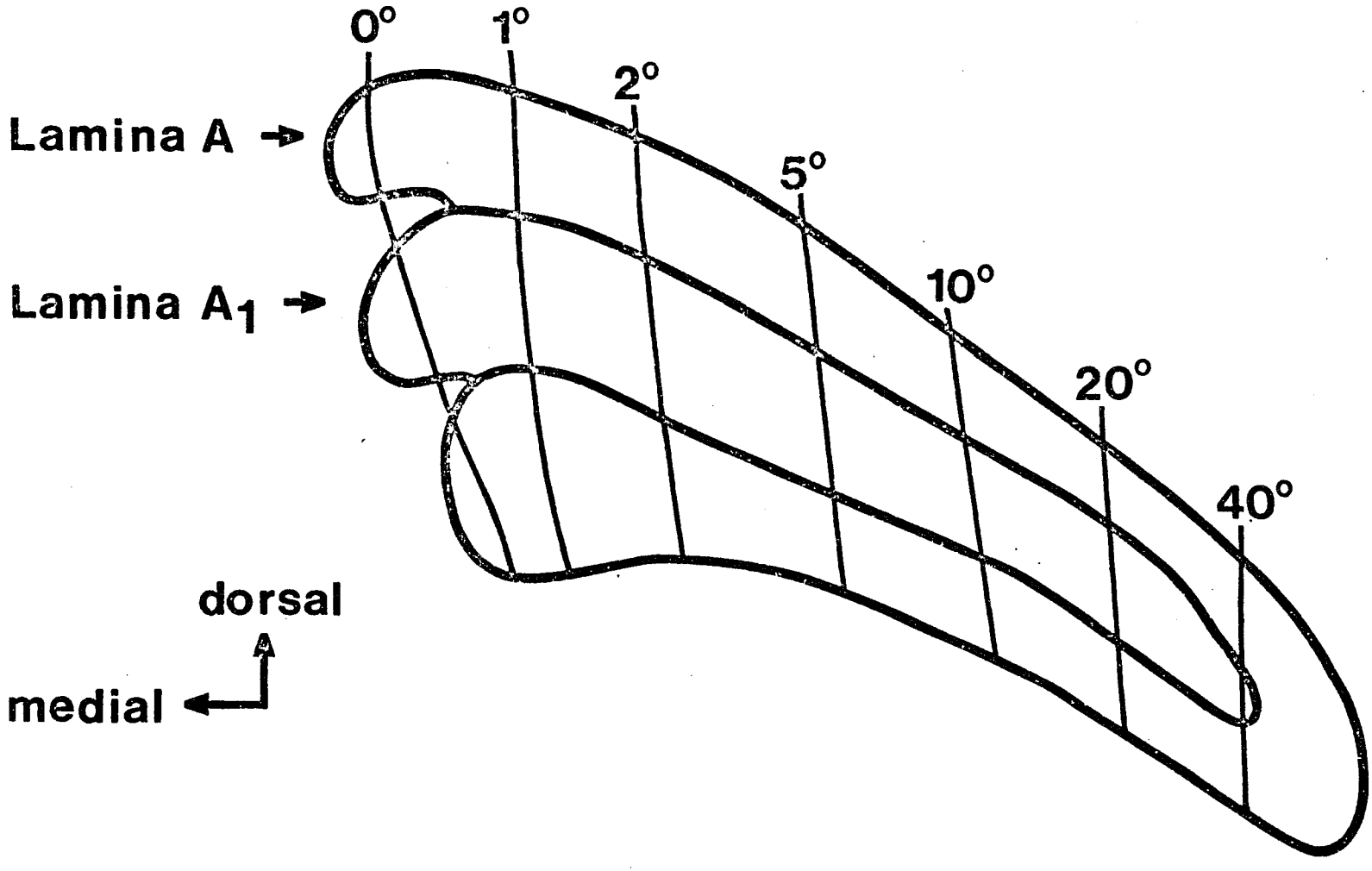


Figure 2. A line drawing of the LGN at the same anterior-posterior level shown in Figure 1. Isoeccentricity lines have been superimposed (after Kaas, et al., 1972; Sanderson, 1971a, 1971b) to show the locations in the LGN from which samples of cell body sizes were taken.


0°
1°
2°
5°
10°
20°
40°
Lamina A
Lamina A_1
dorsal
medial

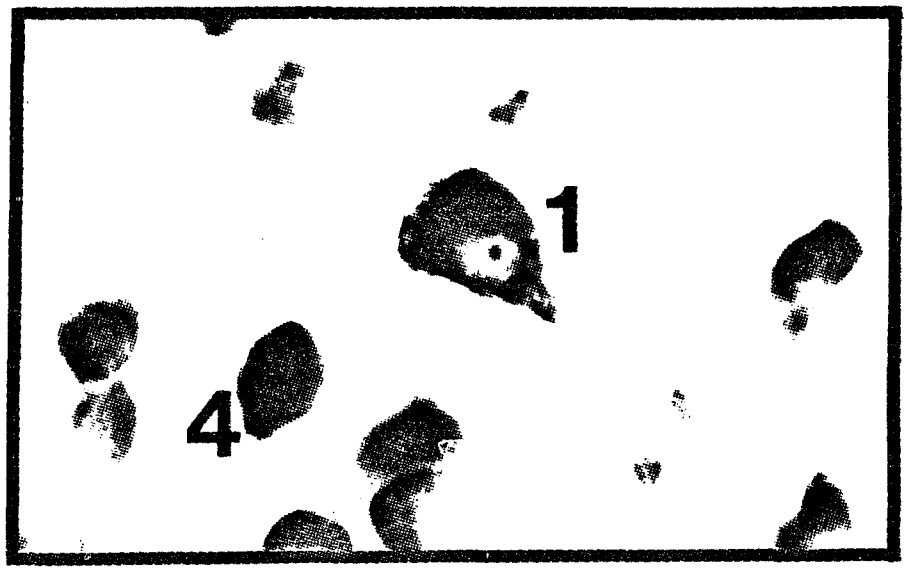
cell body size data. It should be noted that cresyl violet does not stain the cellular membrane, but rather Nissl substance. Such Nissl profiles, however, are commonly used to reflect cell body size (e.g., Hickey, 1980; Hickey, et al., 1977; Kalil, 1978a, 1978b, 1980; Murakami & Wilson, 1983). Further, any change in Nissl profile, even if dissociated from an actual change in cell body size, certainly reflects an alteration in the metabolic activity of a cell.

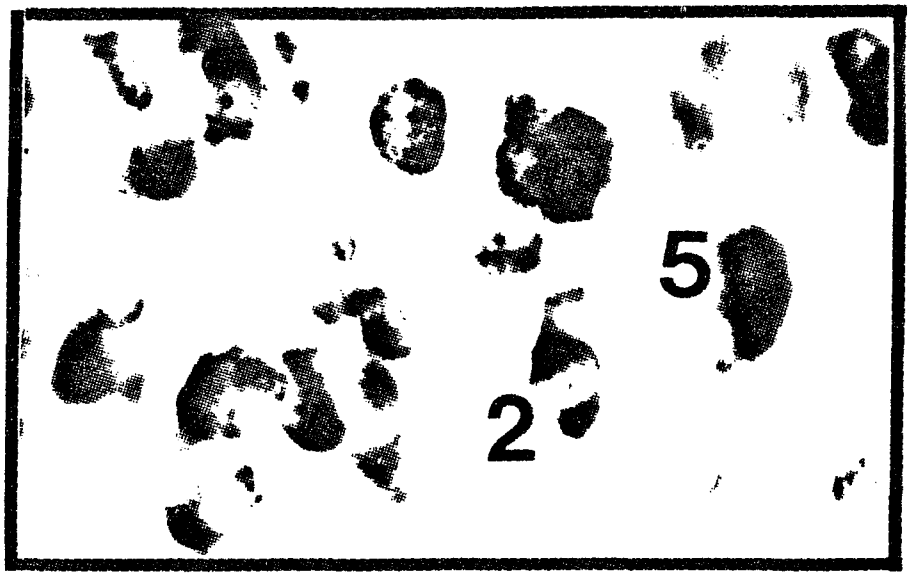
Soma size measurements were made for 100 cells in each of the eccentricity bins in lamina A and lamina A1 in both LGNs. To prevent any possible experimenter biases from affecting cell body drawings, the slides were blind-coded by a disinterested third party. Slides on which the target coronal plane of the LGN were mounted were viewed through an Olympus Vanox microscope with high resolution objective lenses at a magnification X 1,000. An attached drawing tube projected the image seen through the microscope onto a drawing pad where the outlines of cell bodies were traced (i.e., camera lucida drawing). The criterion for including a given cell in the sample was the presence of a well-defined nucleolus (see Figure 3). Cells were sampled throughout the dorsal-ventral extent of each eccentricity bin in each lamina. The drawing of cell outlines always began at the dorsal surface of the lamina. When all cells within the initial field of view were drawn, the slide was moved so that the adjacent field, just ventral of the initial field, came into view. This process continued until the ventral surface

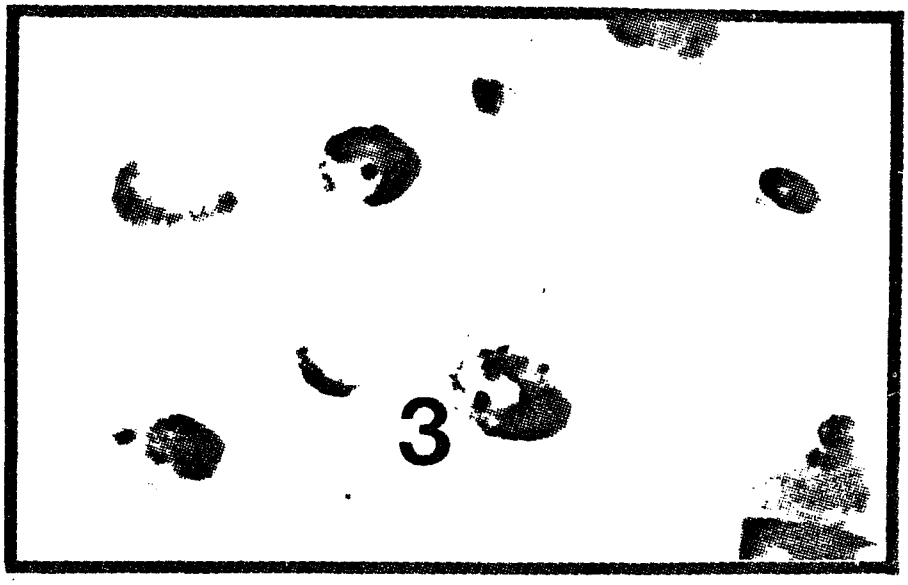
of the lamina was reached. The slide was then moved so that the adjacent lateral field came into view, and drawings continued in a ventral-to-dorsal direction. This continued until 100 cells had been drawn. Drawing 100 cell outlines usually took about two complete traversals of the lamina. Care was taken to move the slide perpendicularly to the long axis of the LGN during the sweeps through the geniculate so that all cell measurements remained within adjacent projection columns (Bishop, et al., 1962; Kaas, et al., 1972; Sanderson, 1971a, 1971b). The outlines of the measured cells were then traced onto the digitized drawing board of a Bioquant II Image Processing System (E. Leitz), which computed areas for each cell. The areas were stored in a computer so that frequency distributions and descriptive statistics for each sample could be printed out later.

The proportions of X- and Y-cells vary as a function of lamina (Hoffmann & Sireteanu, 1977; Hollander & Vanegas, 1977; Mitzdorf & Singer, 1977; Sireteanu & Hoffmann, 1979; Wilson, et al., 1976) and eccentricity (Hoffmann, et al., 1972; Sherman & Spear, 1982). Therefore, cell body size distributions vary depending on layer and eccentricity (Friedlander, et al., 1979, 1981). Therefore, comparisons between experimental conditions will hold layer and eccentricity constant. Finally, since cell body sizes vary from animal to animal independently of experimental manipulation (Cook, Walker, & Barr, 1951; Garey, Fisken, & Powell, 1973; Hickey, et al., 1977; Guillery &

Figure 3. Single LGN cells stained with cresyl violet. As can be seen, cells numbered 1, 2, and 3 have clearly defined nucleoli. Cells numbered 4 and 5, on the other hand, do not. It is important to note, however, that these photomicrographs were taken at particular planes of focus. As cells were measured, the focal plane was moved systematically through the thickness of the tissue within each field of view. Cells 4 and 5, therefore, could have clearly defined nucleoli in focal planes other than the ones represented in these photographs.


1
4


5
2


3

Stelzner, 1970; Wiesel & Hubel, 1963a), cell body sizes are not independent. Consequently, the means of the 100 cells sampled in each geniculate region in each cat were used in the statistical analyses. Statistical comparisons were made using the t-test, with degrees of freedom determined by number of means (i.e., subjects) and not number of cells.

CHAPTER III

RESULTS

Data are reported here for 18,200 cell body measurements made in the lateral geniculate nuclei of thirteen cats. Five of these cats were normally reared control subjects, four were reared with monocular paralysis, and four experienced at least one year of monocular paralysis beginning in adulthood. In each LGN of these cats, 100 cells were measured in each of seven geniculate regions: separately for laminae A and A1 in areas representing 0-5°, 6-20°, and 21-45°; and in the part of lamina A representing the monocular crescent (i.e., 46-90°). Appendix B presents the frequency distributions of cell body sizes for the individual subjects.

In addition to experimental data, Figure 4 presents the mean cell body sizes (±S.E.) for the seven geniculate regions from which measurements were taken in the normal cats. The data from these normal subjects have been collapsed across hemispheres producing a generic LGN. Table 1 gives the mean values for the hemispheres separately, and shows that those averages were very similar. The average cell sizes shown in Table 1 are in good agreement with normal data reported elsewhere (Hickey, 1980; Hickey, et al., 1977; Kalil, 1978a, 1978b, 1980; Spear & Hickey, 1979). It would seem, therefore, that the methods used in the

present study have not produced any systematic measurement errors.

The data in Table 1 also show that cells in lamina A1 are larger, on the average, than cells in lamina A. This relationship has been shown before, but not for the entire horizontal extent of the binocular segment. The present observations show that layer A1 cells are, on average, 5.2% larger than cells in lamina A. Another observation which can be gleaned from the data in Table 1 is that average cell size changes as a function of eccentricity. This relationship is not, however, direct. Cells in the geniculate regions representing 0-5° had an average size of 236.4 μm^2. Cells in regions of the A and A1 laminae representing 6-20° were somewhat larger, with a mean of 248.9 μm^2. This trend was reversed in the a and A1 regions representing 21-45°. Cells in this area had an average size of 218.6 μm^2. This value was significantly smaller than the means for cells in geniculate areas representing 0-5° ($p<.025$) and 6-20° ($p<.005$). Cells in the monocular segment were smaller yet with a mean size of 199.7 μm^2.

Table 1

Mean Cell Sizes in the Various Geniculate

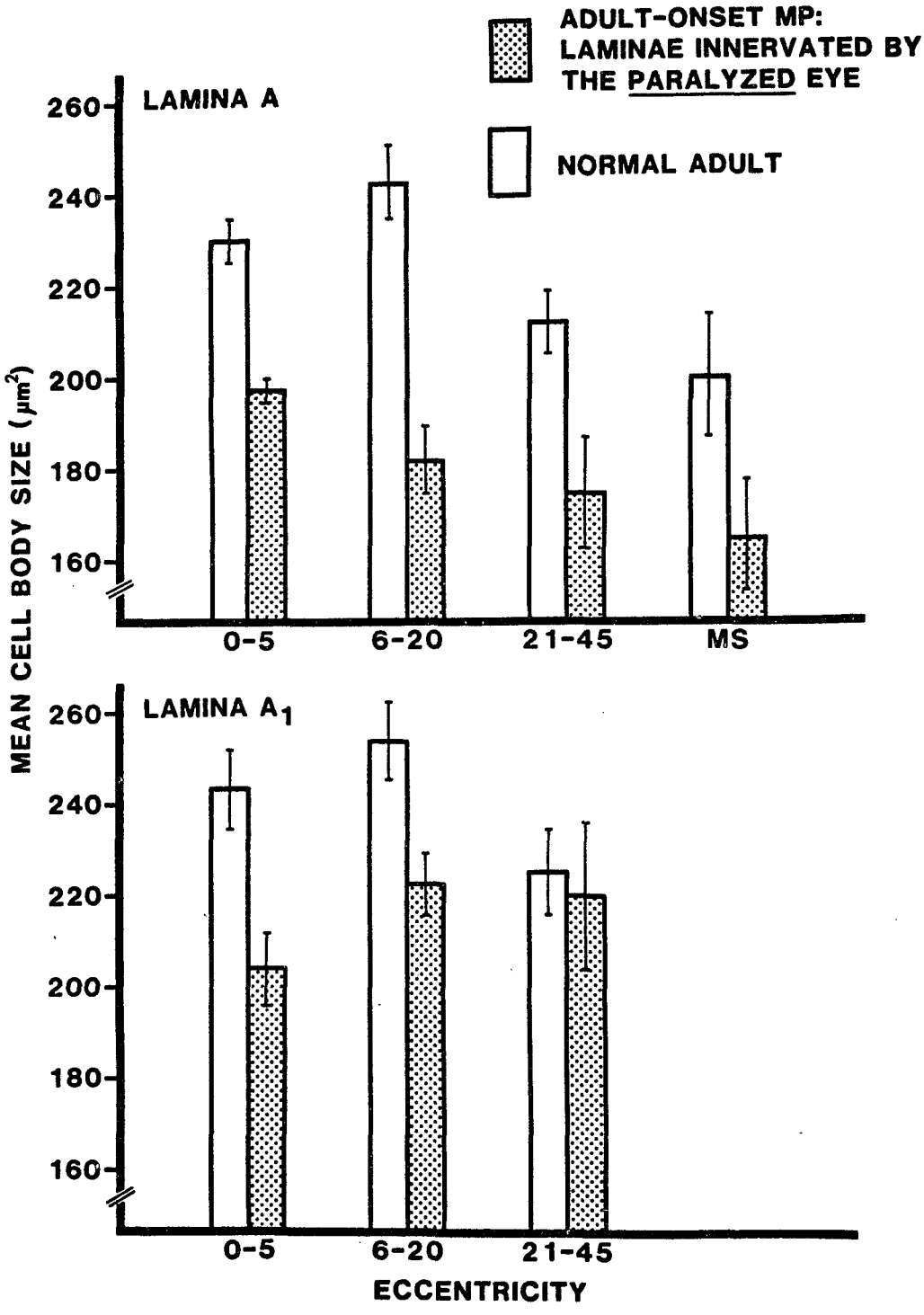
Regions of Normal Cats

	A				A1		
Hemisphere	0-5°	6-20°	21-45°	46-90°	0-5°	6-20°	21-45°
Right	230.0	242.0	216.9	205.8	246.9	250.9	223.3
Left	228.7	245.4	207.5	193.6	239.9	257.3	226.8

In addition to the normal data, Figure 4 presents data taken from laminae innervated by the paralyzed eye in the cats monocularly paralyzed as adults. In the region of lamina A representing 0-5°, the mean cell size of the cats paralyzed as adults was 197.5 μm^2, as compared to a mean of 229.4 μm^2 in the normal adults. This constitutes a shrinkage of 13.9% ($p<.005$). In the portion of this A layer representing 6-20°, the mean cell size in the monocularly paralyzed adult cats was 182.3 μm^2. Relative to the normal value of 243.7 μm^2, this represented an average shrinkage of 25.2% ($p<.005$). Similarly, in the part of lamina A representing 21-45°, the cells in the monocularly paralyzed adults were, with a mean of 175.0 μm^2, 17.5% smaller than those with a mean of 212.2 μm^2 in the normal cats ($p<.025$). Even though the mean cell size in the monocular segment of the monocularly paralyzed adult cats (164.8 μm^2) was 17.5% smaller than normal (199.7 μm^2), this difference was not statistically reliable.

Cell shrinkage was also observed in the A1 lamina innervated by the paralyzed eye after adult-onset monocular paralysis. In the region of the A1 layer representing 0-5°, the average cell size in the monocularly paralyzed adult cats was 205.2 μm^2, relative to 243.4 μm^2 in the comparable laminar region in the normal cats. This 15.7% reduction in average cell size was statistically significant ($p<.025$). Shrinkage was also evident in the part of lamina A1 representing 6-20°. The average cell size of 223.2 μm^2 in the monocularly paralyzed cats was 12.2% smaller than the average of 254.1 μm^2 found in the control subjects ($p<.05$). There was no sign of shrinkage in the region of lamina A1 representing 21-45°. The average cell size of 220.7 μm^2 in the

Figure 4. Histograms of mean cell sizes of LGN cells in laminae innervated by the paralyzed eye after adult-onset monocular paralysis compared to normal. Data from the cats monocularly paralyzed as adults (Adult MP) were taken in laminae innervated by the paralyzed eye (i.e., contralateral lamina A and ipsilateral lamina A1). Data from the normal cats have been collapsed across hemispheres. Mean cell sizes are presented for measurements made in three eccentricity zones (0-5°, 6-20°, and 21-45°) in the binocular segments of the A and A1 laminae, and in the monocular segment.


ADULT-ONSET MP:
LAMINAE INNERVATED BY
THE PARALYZED EYE
NORMAL ADULT
LAMINA A
LAMINA A1
MEAN CELL BODY SIZE (μm²)
260
240
220
200
180
160
0-5
6-20
21-45
MS
ECCENTRICITY

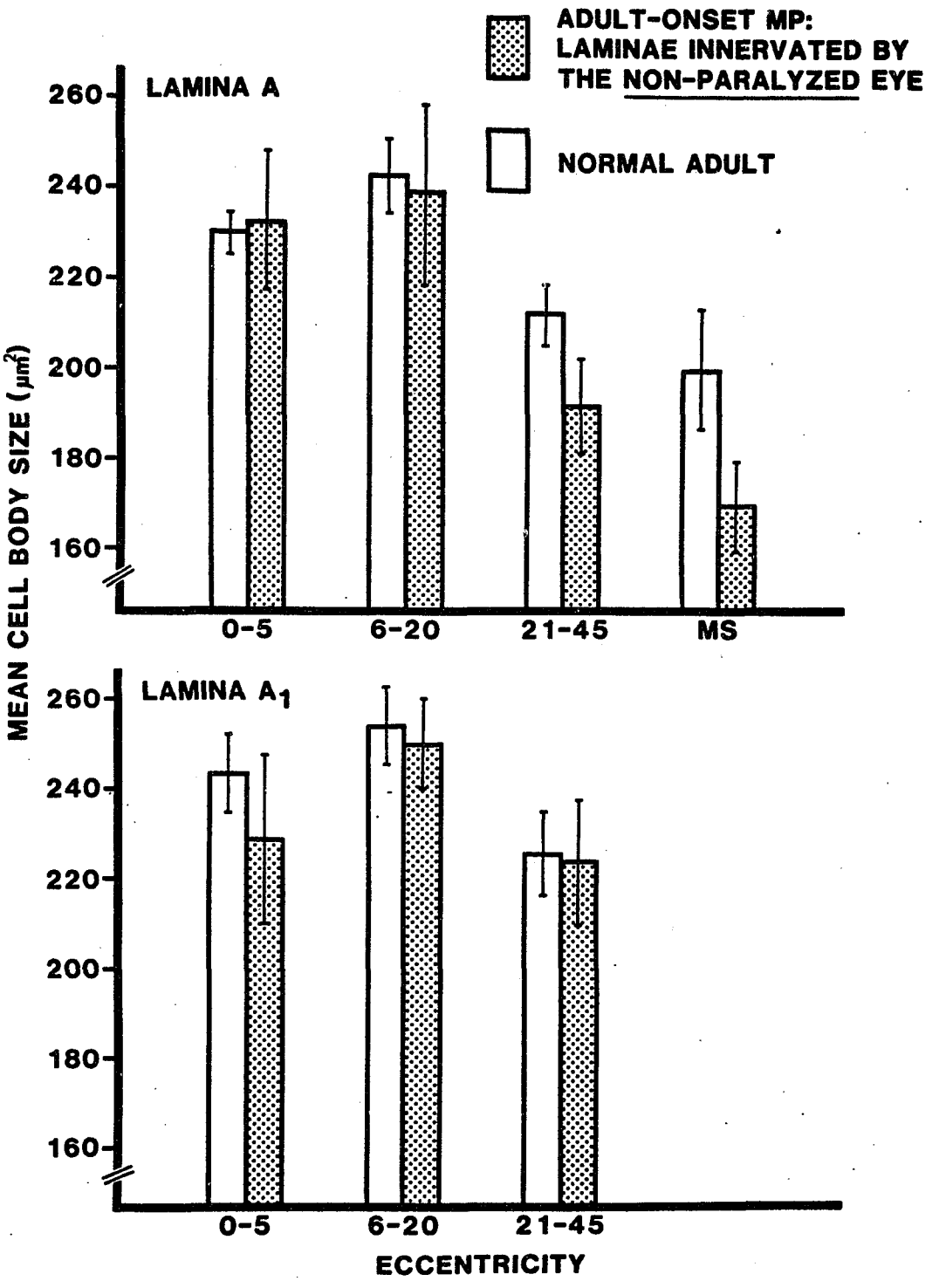
monocularly paralyzed adults was almost identical to the average of 225.0 μm^2 in the normally reared adult cats.

In the LGN laminae innervated by the mobile eye, a prolonged period of adult-onset monocular paralysis was found to have no effect on cell body size. Figure 5 presents the average cell sizes for the normal and monocularly paralyzed adult cats. As can be seen, the differences are

In summary, adult-onset monocular paralysis results in cellular shrinkage in the LGN. This shrinkage is confined to the binocular segment of the laminae innervated by the paralyzed eye. In the A layer, contralateral to the paralyzed eye, shrinkage was evident throughout the binocular segment. In the A1 lamina, ipsilateral to the paralyzed eye, cells were smaller in the region representing $0-20^{o}$, but cells in the portion of this A1 lamina representing $21-45^{o}$ were normal in size.

Figures 6 and 7 present the mean cell size data for cats reared with monocular paralysis and for normal adult cats. Data in Figure 6 are from the laminae innervated by the paralyzed eye (i.e., contralateral lamina A and ipsilateral lamina A1). In the region of lamina A representing $0-5^{o}$, the mean cell size in the cats reared with monocular paralysis was 174.1 μm^2, while in the normal cats this value was 229.4 μm^2. This shrinkage of 24.1% was statistically significant ($p<.005$). In the region representing $6-20^{o}$, the mean of 201.3 μm^2 in the cats reared with monocular paralysis was 17.4% smaller than the mean of 243.7 μm^2 in the normal adults. This shrinkage was also statistically significant ($p<.025$). Similarly, in the region of lamina A representing $21-45^{o}$, the mean of the cats reared with monocular

Figure 5. Histograms of mean cell sizes of LGN cells in laminae innervated by the mobile, non-paralyzed eye after adult-onset monocular paralysis compared to normal. Data from the cats monocularly paralyzed as adults (Adult MP) were taken in laminae innervated by the mobile, unoperated eye (i.e., ipsilateral lamina A and contralateral lamina A1). Data from the normal cats have been collapsed across hemispheres. Mean cell sizes are presented for measurements made in three eccentricity zones (0-5°, 6-20°, and 21-45°) in the binocular segments of the A and A1 laminae, and in the monocular segment.


ADULT-ONSET MP:
LAMINAE INNERVATED BY
THE NON-PARALYZED EYE
NORMAL ADULT
LAMINA A
LAMINA A1
MEAN CELL BODY SIZE (μm²)
260
240
220
200
180
160
0-5
6-20
21-45
MS
ECCENTRICITY

paralysis (163.8 μm^2) was smaller than the mean of the normal cats (212.2 μm^2). This 22.8% reduction in mean cell size was statistically significant ($p<.01$). In contrast to these effects in the binocular segment of the A lamina, infant-onset monocular paralysis had no effect in the monocular segment.

Cell shrinkage was also found in the A1 lamina innervated by the paralyzed eye after infant-onset monocular paralysis. In the region representing 0-5°, the mean cell size in the cats reared with monocular paralysis was, at 190.6 μm^2, 21.7% smaller than the mean of 243.4 μm^2 in the normal cats ($p<.025$). In the representation of 6-20°, the mean cell size in the cats reared with monocular paralysis was 207.5 μm^2. This was 18.3% smaller than the mean of 254.1 μm^2 in the normal cats ($p<.025$). The portion of this lamina A1 representing 21-45° was also affected by rearing with monocular paralysis. The average cell size in the monocularly paralyzed cats (183.2 μm^2) was 22.4% smaller than normal (225.0 μm^2; $p<.01$).

Figure 7 presents data from the laminae innervated by the mobile eye in the cats monocularly paralyzed as infants. In the region of this lamina A representing 0-5°, the average cell size in the monocularly paralyzed cats was 186.1 μm^2. This represented a shrinkage of 18.9% relative to the normal mean of 229.4 μm^2 ($p<.005$). In the area of this A layer containing the representation of 6-20°, the average cell size in the cats reared with monocular paralysis was 204.0 μm^2, while the normal value was 243.7 μm^2. This difference shows a relative shrinkage of 21.7%, and was statistically significant ($p<.025$). Similarly, in the area of lamina A representing 21-45°, the mean cell size of the

Figure 6. Histograms of mean cell sizes of LGN cells in laminae innervated by the paralyzed eye after infant-onset monocular paralysis paralysis compared to normal. Data from the cats reared with monocular paralysis (Kitten MP) were taken in laminae innervated by the paralyzed eye (i.e., contralateral lamina A and ipsilateral lamina A1). Data from the normal cats have been collapsed across hemispheres. Mean cell sizes are presented for measurements made in three eccentricity zones (0-5°, 6-20°, and 21-45°) in the binocular segments of the A and A1 laminae, and in the monocular segment.

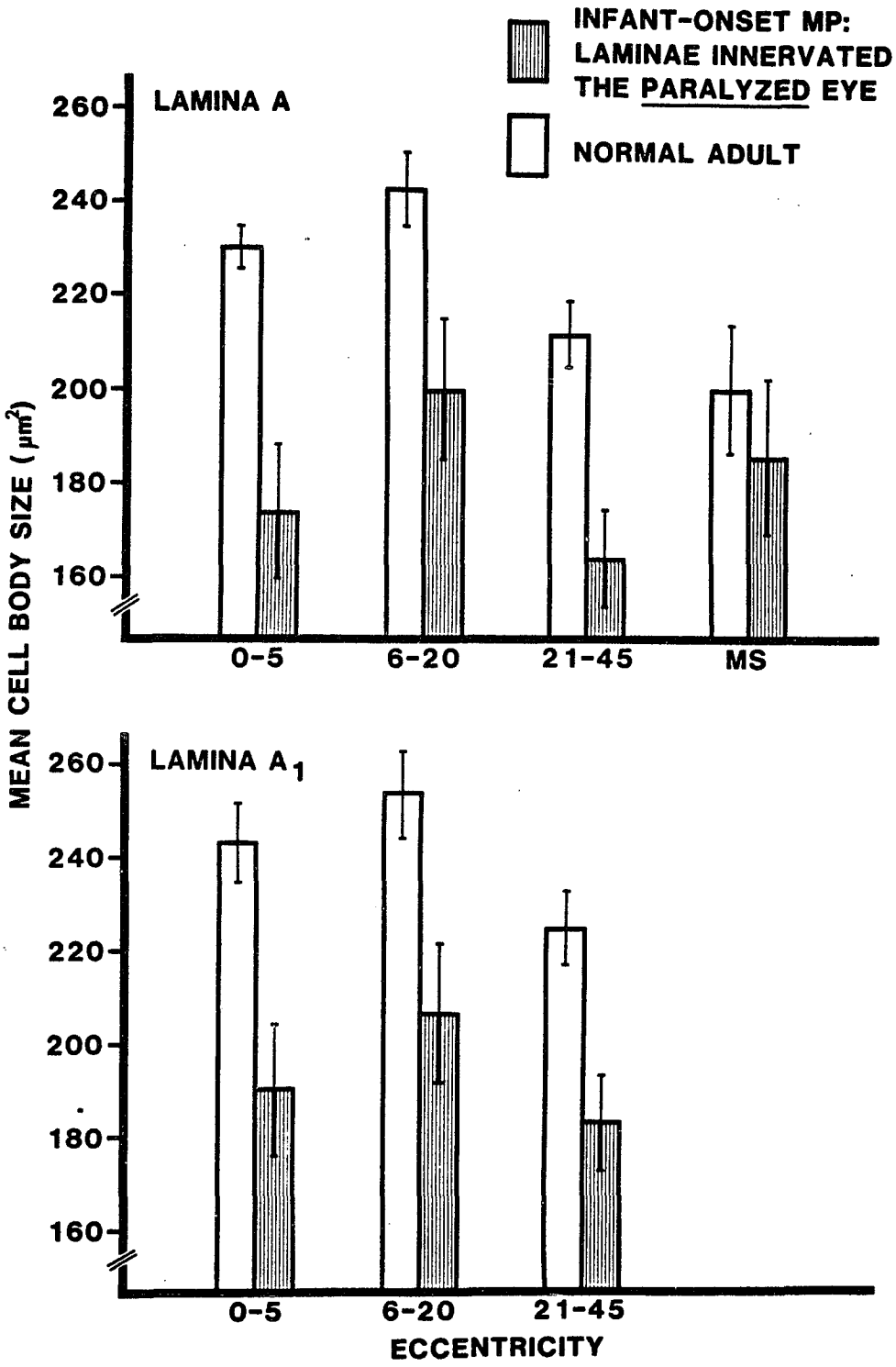
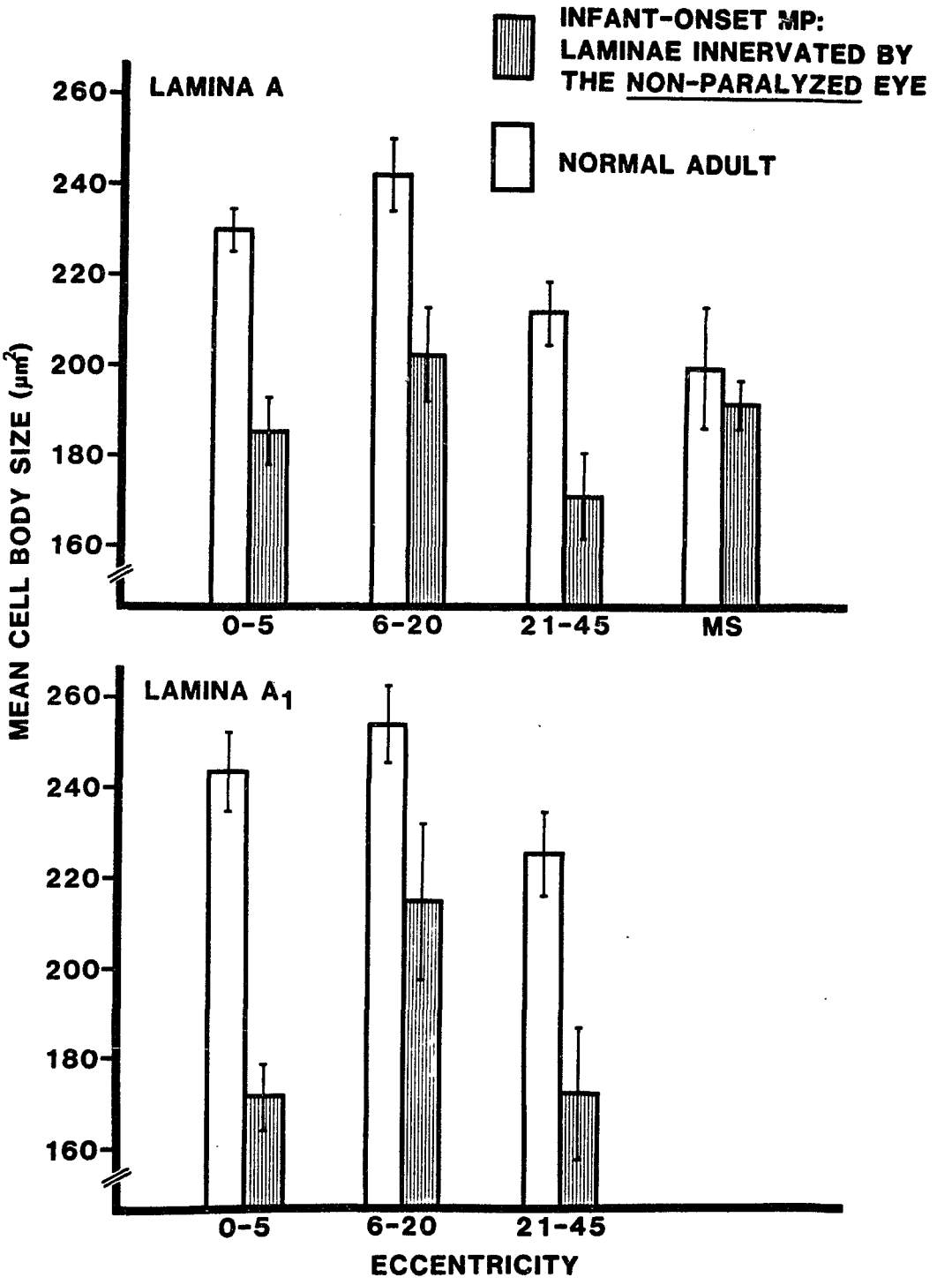

INFANT-ONSET MP:
LAMINAE INNERVATED BY
THE PARALYZED EYE
NORMAL ADULT
LAMINA A
LAMINA A1
MEAN CELL BODY SIZE (μm²)
260
240
220
200
180
160
0-5
6-20
21-45
MS
ECCENTRICITY

Figure 7. Histograms of mean cell sizes of LGN cells in laminae innervated by the mobile, non-paralyzed eye after infant-onset monocular paralysis compared to normal. Data from the cats reared with monocular paralysis (Kitten MP) were taken in laminae innervated by the mobile, unoperated eye (i.e., ipsilateral lamina A and contralateral lamina A1). Data from the normal cats have been collapsed across hemispheres. Mean cell sizes are presented for measurements made in three eccentricity zones (0-5°, 6-20° and 21-45°) in the binocular segments of the A and A1 laminae, and in the monocular segment.


INFANT-ONSET MP:
LAMINAE INNERVATED BY
THE NON-PARALYZED EYE
NORMAL ADULT
LAMINA A
LAMINA A1
MEAN CELL BODY SIZE (μm²)
260
240
220
200
180
160
0-5
6-20
21-45
MS
ECCENTRICITY

monocularly paralyzed cats (173.5 μm^2) was 18.2% smaller than the normal average (212.2 μm^2; $p<.025$). On the other hand, the average cell size in the monocular segment of cats reared with monocular paralysis (192.5 μm^2) was very close to the normal mean of 199.7 μm^2.

In the A1 lamina, innervated by the mobile eye, cells in the region representing 0-5° had a mean size of 172.6 μm^2 in the cats reared with monocular paralysis. This was 29.1% smaller than the normal average cell size for this geniculate area (243.4 μm^2; $p<.0005$). In the area of this A1 lamina containing the representation of 6-20°, the mean cell size in the cats monocularly paralyzed as kittens was 216.6 μm^2. This value was 14.8% smaller than the normal mean of 254.1 μm^2, but was not a statistically significant difference. The area of this A1 lamina representing 21-45° had an average cell size of 174.5 μm^2 in the cats which underwent monocular paralysis as infants. This was 22.4% smaller than the normal mean of 225.0 μm^2, and was statistically significant ($p<.025$). In the laminae innervated by the mobile eye, therefore, the morphological effects of infant-onset monocular paralysis differed dramatically from those of cats monocularly paralyzed as adults. While no shrinkage was observed in any of these laminar regions after adult-onset monocular paralysis, rearing cats with monocular paralysis produced shrinkage throughout the binocular segment (though insignificantly so in the representation of 6-20° in lamina A1). It would appear, therefore, that LGN morphology responds in a strikingly

different manner to monocular paralysis depending upon the age of the animal at the time the eye is immobilized.

Based on comparisons with normal adult cats, adult-onset monocular paralysis had dramatically different effects depending upon whether the lamina was innervated by the paralyzed or mobile eye. Similar comparisons involving the cats monocularly paralyzed as kittens show that large differences in the response of the various laminae depending upon which eye provided innervation were not present. Could there be some more subtle differences? The overall mean from the binocular segment of laminae innervated by the paralyzed eye (i.e., contralateral lamina A and ipsilateral lamina A1) was 186.8 μm^2 in the cats reared with monocular paralysis. The mean for the laminae innervated by the mobile eye was 189.5 μm^2. This small (1.4%) difference is obviously attributable to chance. This outcome is unaltered if the A and A1 laminae are compared separately. There is, therefore, no suggestion in the present data that LGN laminae were affected differentially by infant-onset monocular paralysis depending upon which eye (i.e., mobile or paralyzed) provided the innervation.

One final question to be addressed with the present data is whether or not there is support for the hypothesis that both X- and Y-cells are lost after infant-onset monocular paralysis, while only X-cells are affected by adult-onset monocular paralysis. To approach this question, those laminar regions where the adult-onset cats differed from normal

can be compared with the same geniculate regions in the animals which underwent monocular paralysis as infants. If the morphological effects in the cats monocularly paralyzed as adults are correlated with the loss of X-cells in those laminae, then the hypothesized additional Y-cell loss with infant-onset monocular paralysis might be expected to produce additional morphological effects corresponding to the Y-cell loss. The overall mean of cell sizes in the laminar regions where shrinkage followed adult-onset monocular paralysis (i.e., 0-45° in contralateral layer A and 0-20° in ipsilateral layer A1) was 196.6 μm^2. The comparable value from the animals paralyzed as infants was 187.5 μm^2. This small difference (4.6%) was not significant, and this result was unaffected by treating the A and A1 laminae separately. It is possible, however, that a difference is not found between these conditions because of a ceiling effect. That is, in preparations not involving deafferentation, there could be some maximum percentage of shrinkage. The effects of the adult-onset preparation could be so severe, relative to the hypothetical maximum effect, that any additional shrinkage would be difficult to detect against the background.

Another way to approach this question is to compare these data based on the relative numbers of large cells in the two groups. That is, it has been demonstrated that Y-cells are larger than X-cells (Friedlander, et al., 1979, 1981). If infant-onset monocular paralysis does have an effect on Y-cells, there may be fewer large cells in the

geniculates of those cats, relative to the cats paralyzed as adults. The average proportion of large (i.e., >250 μm^2) cells in the subjects which were monocularly paralyzed as kittens was 14.8%. The comparable value in the cat paralyzed as adults was 21.6%. This 31.5% reduction in the proportion of large cells in the infant-onset, relative to adult-onset, subjects was significant ($p<.025$). These data are, therefore, consistent with the hypothesis that the cats reared with monocular paralysis have suffered a loss of Y-cells.

In summary: (1) data from the normal adult cats are consistent with other normal data reported in the literature. (2) These same data have confirmed the observations of others that average cell size is larger in lamina A1 than in lamina A, and (3) have extended those previous observations by showing that this relationship exists throughout the binocular segment. (4) The data from the normal cats have also shown that while average cell sizes are different for geniculate regions representing different eccentricities, there is not a simple direct relationship between cell size and eccentricity. (5) Cellular shrinkage in cats monocularly paralyzed as adults was found only in laminae innervated by the paralyzed eye, and (6) only in parts of the binocular segment of those laminae. (7) Since X-cells are lost in the A and A1 laminae of both hemispheres regardless of the status of the innervating eye, these data show that the X-cell loss and the morphological shrinkage which result from adult-onset monocular

paralysis are dissociated. (8) In cats monocularly paralyzed as infants, cells were shrunken throughout the binocular segments of laminae A and A1 in both hemispheres. In the region of the A1 lamina, innervated by the mobile eye, which contained the representation of 6-20° cells in the cats monocularly paralyzed as infants were found to not differ from normal. One possibly aberrant subject in the experimental group was responsible for the lack of significance. When this comparison was performed using the Mann-Whitney test, the difference was found to be statistically reliable ($p<.05$). This observation, together with the overall pattern of shrinkage in the cats reared with monocular paralysis, suggests that cells in the region were probably affected by this rearing procedure. Since no theoretical explanation for the absence of an effect only in this region exists, and since my principal concern is with the overall pattern of shrinkage, I will treat this difference as significant throughout the Discussion. (9) These morphological effects may be associated with the physiological consequences of infant-onset monocular paralysis. (10) Finally, it appears that the shrinkage in the animals reared with monocular paralysis supports the hypothesis that both X and Y-cells are affected by this manipulation.

CHAPTER IV

DISCUSSION

The present experiments have assessed the morphological effects of prolonged periods of infant- and adult-onset monocular paralysis in the lateral geniculate nucleus. These morphological data consist of 1400 cell body size measurements in each of 13 cats. A prolonged period of adult-onset monocular paralysis was found to produce shrinkage of cells in parts of the LGN laminae innervated by the paralyzed eye. The same period of monocular paralysis beginning in infancy, however, produced a different pattern of effects. Infant-onset monocular paralysis was found to result in reductions in the average cell body size of neurons in virtually all portions of the binocular segments of the A and A1 laminae in both hemispheres (i.e., whether the innervating eye was paralyzed or mobile). Conclusions concerning the effects of adult- and infant-onset monocular paralysis were reached based largely on comparisons of the cell body sizes in the LGNs of cats in these two experimental conditions with those of normal adult cats. It was, therefore, necessary to measure cell body sizes in normally-reared cats as well. These data will be discussed first.

Normal Cats

Data from normally-reared adult cats were needed in the present experiment for the sake of comparison. These data may also be used, however, to establish the reliability of the findings reported here. It is known that cells in layer A1 are, on the average, larger than cells in layer A (Guillery & Stelzner, 1970; Hickey, 1980; Kalil, 1980). This relationship exists for two reasons. First, lamina A1 contains more Y-cells than lamina A (Hoffmann & Sireteanu, 1977; Mitzdorf & Singer, 1977; Wilson, et al., 1976), and Y-cells are larger than X-cells (Friedlander, et al., 1979, 1981; Hollander & Vanegas, 1977; LeVay & Ferster, 1977). Secondly, Friedlander, et al. (1981) have shown that both X- and Y-cells in lamina A1 are larger than their counterparts in lamina A. Detecting a relationship of this sort provides a relative, within-subject measure of validity. Throughout the binocular segment of the five normal cats in which data were collected, lamina A1 cell sizes in the present study were, on the average, 5.2% larger than cells in lamina A. This relationship held in all eccentricity zones in both hemispheres. Further, the absolute sizes of cells in the normal cats presented here can be compared with those reported by others. The normal values reported here (see Table 1) are in good agreement with data from normal cats published elsewhere (Guillery, 1966; Hickey, 1980; Hickey, et al., 1977; Kalil, 1978a, 1978b, 1980; Spear & Hickey, 1979). To the extent that consistency

with these previous reports implies validity, it would appear that the cell body measurements in the present experiments are valid.

These data constitute the first report of the relationship of cell body size to horizontal eccentricity in the normal adult cat. Cell body measurements in the normal cats in the present experiment showed that cells in the most central LGN regions sampled (i.e., 0-20°) were larger than those in the more peripheral regions (i.e., 21-45°, and the monocular segment). These findings are at variance with the suggestion of Friedlander, et al. (1981) that cell size tends to increase with increasing eccentricity. Their sample, however, consisted of only 47 cells, and included very few from geniculate regions representing eccentricities in excess of 25°. A possible basis for the suggestion of Friedlander, et al. (1981) regarding cell size gradients in the LGN can be seen in the subset of the present data collected in portions of the LGN representing the central 20°. Within this more restricted range of eccentricities, the present sample also was characterized by a slight tendency for cells to become larger with increases in eccentricity. That is, the average cell sizes in the regions of the LGN representing 6-20° were slightly (and not significantly) larger than the mean cell sizes in parts of the geniculate representing 0-5°. However, the cells in the regions of the LGN representing 0-20° in the normal cats studied here were significantly larger than those in the more peripheral locations. Therefore, if a size gradient does exist across the entire

LGN, the present data clearly show that cells become significantly smaller with increasing eccentricity, and not larger as suggested by Friedlander, et al. (1981) based on their more limited sample.

The fact that average cell size does not increase with increasing eccentricity within the geniculate has implications for the relationship between cell size and physiological class. Friedlander, et al. (1981) recorded LGN neurons intracellularly and, after classifying them physiologically, labeled them with horseradish peroxidase. With this technique they could directly correlate physiology with morphology. Based on their sample, they concluded that: (1) all cells with areas less than 250 μm^2 were X-cells, (2) all cells with areas greater than 450 μm^2 were Y-cells, and (3) cells with areas between 250 and 450 μm^2 were roughly equally divided between X- and Y-types. If these size categories were strictly adhered to by X- and Y-cells throughout the LGN, however, peripherally located cells would have to be, on the average, larger than more centrally located cells. That is, since Y-cells become proportionately more plentiful at greater eccentricities (Hoffmann, et al., 1972; Sherman & Spear, 1982) and are larger than X-cells (Friedlander, et al., 1979, 1981; Hollander & Vanegas, 1977; LeVay & Ferster, 1977), one might have expected average cell size to increase with increasing eccentricity. Data from the normally-reared cats in the present experiment provide no support for this expectation. On the contrary, it is clear that the sizes of X- and/or Y-cells must

change with eccentricity. These changes could be systematic, with both X- and Y-cells becoming comparably smaller, or the relationship between cell size and physiological class demonstrated so elegantly by Friedlander, et al. (1981) might break down completely in parts of the LGN representing greater eccentricities. The average cell size in the monocular segment of the normal cats in the present study, and in other reports (Hickey, 1980; Hickey, et al., 1977; Kalil, 1978a, 1978b, 1980; Spear & Hickey, 1979), were consistently smaller than cells in any of the binocular segment locations even though Y-cells comprise a much larger proportion of the population in that region (Hoffmann, et al., 1972; Sherman & Spear, 1982), relative to more central locations. It is clear, therefore, that Y-cells, at least, do become smaller in the more peripheral parts of the LGN. To the extent that the present data do conflict with those of Friedlander, et al. (1981), the accumulation of additional data of the type they collected, in larger numbers, and throughout a wider area should provide a resolution.

Adult-onset Monocular Paralysis

In the present experiment, cell body sizes were measured in the lateral geniculate nuclei of cats which had been monocularly paralyzed for at least one year as adults. These measurements showed that the morphological shrinkage which did follow prolonged adult-onset monocular paralysis was confined to the binocular segments of the laminae

innervated by the paralyzed eye. Shrinkage was found throughout all of the binocular segment of the A layer innervated by the paralyzed eye (i.e., 0-45°), but was detectable only in that part of the A1 layer representing 0-20°. These results have confirmed and extended some of the observations of Garraghty, et al. (1982) who reported some morphological shrinkage in the LGN after just two weeks of monocular paralysis. Those results, which had been the first demonstration of such cellular shrinkage following an adult-onset visual perturbation, were less definitive than the present ones because data were collected only in regions of the geniculate representing 6-20° and the monocular segment. The greater number of eccentricity zones studied in the present experiment provides more information about the pattern of the morphological consequences of adult-onset monocular paralysis.

The fact that cellular shrinkage is found only in laminae innervated by the paralyzed eye raise the possibility that the shrinkage is due to traumatic consequences arising from the monocular paralysis. Perhaps some accidental injury associated with the surgery resulted in a slight anterograde transynaptic degeneration effect (Cook, et al., 1951; Cowan, 1970). Cook, et al. (1951) demonstrated that anterograde degenerative effects require at least one month to become evident and about four months to run their course. While the cats in the present experiment were monocularly paralyzed for at least one year, and, therefore, were subject to the manifestation of any anterograde

degeneration, those for which data were reported previously (Garraghty, et al., 1982) experienced only two weeks of monocular paralysis. Not only was the time course in those animals insufficient to show anterograde degeneration (Cook, et al., 1951), but the magnitude of the effects in those cats (about 10%) was comparable to the present ones (about 12%). The methods used by Cook, et al. (1951), however, were less sensitive than those employed in the present study. It remains possible, therefore, that degenerative effects might occur more quickly than they suggested, and perhaps account for the present results and those of Garraghty, et al. (1982). Two observations argue against this possibility. First is the observation that not all geniculate regions innervated by the paralyzed eye demonstrated shrinkage. That is, cells in the region of lamina A1 representing 21-45°, and cells in the monocular segment were found to be normal in size. It seems unlikely that these areas would be spared if the morphological effects of monocular paralysis were due simply to anterograde transynaptic degenerative shrinkage secondary to trauma. Finally, it should be emphasized that monocular paralysis is accomplished by transecting cranial nerves III, IV, and VI. None of these nerves provides innervation to the LGN or the retina. Any anterograde transynaptic degenerative effects would imply that nerve II (i.e., the optic nerve) or the eye itself was injured. The surgical procedure employed by Salinger (Garraghty, et al., 1982; Salinger, et al., 1977b) minimizes

the probability of any such injury since nerve II and the eye remain encased in bone. Finally, since the dural covering of the brain is not breached during the surgery, there is seemingly no opportunity to inflict direct damage to either the optic tract or the LGN itself. It seems unlikely, therefore, that the present results could arise simply from surgical trauma.

The cell shrinkage after adult-onset monocular paralysis must arise due to the operation of a mechanism which is sensitive to some stimulus component of monocular paralysis. Since a component analysis has not been performed on these morphological effects, however, it is not possible to identify the factor(s) which trigger the mechanism. It does seem clear, however, that this mechanism must be sensitive to disruptions in the normal pattern of binocular stimulation, since cell size changes after monocular paralysis are confined to the binocular segment.

Infant-onset Monocular Paralysis

The present data taken from cats reared with monocular paralysis have shown that cells were shrunken throughout the binocular segments of the A and A1 laminae in both hemispheres whether the innervating eye was paralyzed or mobile. These observations constitute the first report of cell body size reductions in LGN laminae innervated by a "normal" eye using a unilateral visual perturbation. In no other instance has a

unilateral visual insult beginning in infancy been reported to result in any deleterious morphological effects in LGN layers innervated by the nonmanipulated eye. The presence of an effect in laminae innervated by the mobile eye suggests that the reduced cell size cannot be attributed to surgical trauma.

As pointed out in the Results, cells in the region of the LGN lamina A1 innervated by the mobile eye representing 6-20° were found initially to not differ from normal. Reanalysis with the Mann-Whitney statistic, however, did find a reliable difference. This latter observation, together with the overall pattern of shrinkage in the cats reared with monocular paralysis, makes it seem likely that cells in this geniculate region were affected by this rearing procedure, particularly since no theoretical explanation for the absence of an effect only in this region exists. Keeping this caveat in mind, I shall treat this difference as significant throughout the Discussion.

The similarity of the stimulus disruptions associated with monocular paralysis to those accompanying other abnormal rearing conditions prompts one to wonder why their effects differ. Monocular paralysis consists of a complex of stimulus disruptions arising from the paralysis of the intrinsic and extrinsic ocular muscles. Unilateral paralysis of the intrinsic muscles alone accomplished by means of atropine infusions (i.e., penalization) simulates the clinical defect of anisometropia. Unilateral paralysis of the extrinsic muscles can be

simulated by transecting the extraocular muscle tendons of one or more of the eye muscles (strabismus). Rearing cats with either strabismus or anisometropia has been reported to have morphological effects in the LGN which are confined to laminae innervated by the manipulated eye (Ikeda, et al., 1977; Ikeda & Tremain, 1978a; Tremain & Ikeda, 1982). Since monocular paralysis is a combination of these components, it is not immediately obvious why the pattern of morphological effects should differ so dramatically. A closer look at those previous data provides a possible resolution of this paradox.

Before reassessing the morphological data taken from cats reared with artificial strabismus (Ikeda, et al., 1977; Tremain & Ikeda, 1982), however, a brief digression outlining the emergence of significant design issues in analyzing and interpreting cell body size data is required. Wiesel and Hubel (1963a) initially reported the morphological effects of infant-onset monocular deprivation using the nondeprived laminae in the monocularly deprived cats as the control observation. This method of analysis neutralized the contribution of large between-subject differences in cell body size distributions to the experimental outcome, and had the ethical advantage of reducing the total number of subjects required for the experiment. As mentioned previously, Wiesel and Hubel (1963a) found that cells in the deprived laminae of monocularly deprived cats were smaller than "normal" (i.e., smaller than cells in the nondeprived laminae). Guillery (1972) was the

first to suggest that monocular deprivation might cause not only atrophy of cells in the deprived laminae but also hypertrophy of cells in the nondeprived laminae. In light of this possibility, the reports on the morphological effects of monocular deprivation then in the literature (Guillery & Stelzner, 1970; Kupfer & Palmer, 1964; Wiesel & Hubel, 1963a) could have been interpreted solely on the basis of hypertrophy of cells in the nondeprived laminae. This possibility obviously had profound implications for the hypothesized mechanisms proposed to control cell body size in the LGN as a function of experience. Hickey, et al. (1977) were the first to directly assess the consequences of monocular deprivation on the morphology of cells in deprived and nondeprived laminae. They accomplished this by comparing the average cell size of the deprived and nondeprived laminae of a group of monocularly deprived cats with the matched laminae from a group of normal adult cats. In doing so, Hickey, et al. (1977) confirmed Guillery's (1972) suspicion by finding that not only were cells in the deprived laminae of the monocularly deprived cats smaller than the normal controls, but also that cells in the nondeprived laminae were larger than normal (but see Kalil, 1980). A similar result has been obtained more recently in cats treated with monocular injections of tetrodotoxin, a preparation which eliminates action potentials in optic nerve axons arising in the injected eye (Kuppermann, 1983). These data from monocularly deprived (Hickey, et al., 1977) and tetrodotoxin-

treated cats (Kuppermann, 1983) have shown that the layers innervated by the nondeprived, "normal" eye can be affected by a unilateral visual perturbation. This surprising result has effectively denied researchers the luxury of using subjects as their own controls in such studies. This design contraint has been adhered to in the present experiment for the reasons mentioned above and because of the reported bilateral effects of infant-onset strabismus (Chino, et al., 1983, Cynader & Harris, 1980; Holopigian & Blake, 1983) and monocular paralysis (Salinger, et al., 1978).

The two reports in the literature involving the effects of infant-onset strabismus on the morphology of LGN cells in cats (Ikeda, et al., 1977; Tremain & Ikeda, 1982) did not use normally-reared cats as controls. Rather, in these instances the average cell size for some region of the LGN laminae innervated by the squinted or atropinized eye was compared to the average size of cells in the matched regions of the layers innervated by the nondeviated or unpenalized eye. In other words, these authors (Ikeda, et al., 1977; Tremain & Ikeda, 1982) assumed that infant-onset strabismus and anisometropia have no effect on the morphology of cells in the LGN laminae innervated by the normal, untreated eye, and, consequently, used these layers as within-animal controls. For example, Tremain and Ikeda (1982) measured cells in the central portions of laminae A and A1 in both LGNs after unilateral squint or penalization. They then combined the data by eye so that data

from the A layer contralateral to the experimental eye were pooled with data from the ipsilateral lamina A1. These data were then compared to those from the contralateral A1 and ipsilateral A. In addition to their six experimental subjects, Tremain and Ikeda (1982) also reported data from one normal cat. Analyzing their data in this fashion, Tremain and Ikeda (1982) found that three of their six experimental cats displayed shrinkage in the lamina innervated by the deviated or atropinized eye.

Interestingly, if the cell size data from the cats reared with monocular paralysis had been analyzed using the laminae innervated by the mobile eye as the control, one would have concluded that infant-onset monocular paralysis had no effect on LGN cell morphology. Alternatively, in using data from normal cats as controls, it is clear that infant-onset monocular paralysis had effects on cells in all geniculate laminae. Likewise, when the average cell sizes from Tremain and Ikeda's (1982) experimental subjects are compared with the average cell sizes from the one normal cat included in that report, some shrinkage is present in all laminae in all of their experimental cats, whether the innervating eye was squinted, atropinized, or normal. Therefore, their data become more consistent when data from normal cats are used as controls. It is interesting to note that while individual data are not reported in Ikeda, et al. (1977), the pooled averages for the laminae innervated by the deviated or normal eye are all much smaller (i.e., ranging from about 130 to 175 μm^2) that the normal data

reported here or elsewhere in the literature (Garraghty, et al., 1983; Hickey, 1980; Hickey, et al., 1977; Kalil, 1978a, 1978b, 1980; Spear & Hickey, 1979), and, in fact, smaller that the data from the one normal cat reported in Tremain and Ikeda (1982). These observations raise the possibility that the absence of bilateral morphological effects after infant-onset strabismus or atropinization reported by Ikeda, et al. (1977) and Tremain and Ikeda (1982) are simply an artifact of the analytic technique they used in interpreting their data. It may be the case, therefore, that the present data from cats reared with monocular paralysis are consistent with those of Tremain and Ikeda (1982), and, consequently, less unique than one might initially imagine. If infant-onset monocular paralysis, strabismus, and penalization do produce similar morphological effects, one would not be greatly surprised since common stimulus disruptions are involved.

A Comparison of Monocular Paralysis and Monocular Deprivation in Infants

Infant-onset monocular paralysis results in cellular shrinkage throughout the binocular segments of the A and A1 laminae in both hemispheres whether the innervating eye is paralyzed or mobile. This pattern of shrinkage is dramatically different from that found after infant-onset monocular deprivation where shrinkage is found only in the binocular segments of the laminae innervated by the deprived eye. Cells

are not shrunken in the layers receiving inputs from the open eye. Since duration and age of onset are comparable, the differences in the effects of infant-onset monocular paralysis and monocular deprivation would seemingly have to be due to differences in the nature of the stimulus disruptions associated with these two forms of deprivation.

Under normal conditions, the inputs of each eye are equally strong and each eye contributes roughly half of the afferentation to cortex. In cats reared with monocular deprivation, the nondeprived eye enjoys a competitive advantage, and, consequently, the deprived eye can drive very few cells, and its afferents occupy less of cortex. There are, therefore, functional and structural signs of the competitive imbalance (e.g., see Sherman & Spear, 1982) which apparently arises simply because the inputs of the two eyes are not equally strong (Blakemore, 1976). With a monocularly paralyzed (or strabismic) cat, on the other hand, the large imbalance in the strength of the inputs from the two eyes characteristic of monocular deprivation is not present. Rather, the inputs of the two eyes are equally strong but the brain may be incapable of fusing them into a single, cyclopean image due to the misaligned visual axes. That is, inputs are normally suppressed in the production of binocular, single vision. With monocular paralysis or strabismus, however, the visual system may be confronted with inputs which exceed the normal range of disparities (i.e., diplopia). It is possible that the mechanism which is normally involved in the suppression of inputs

which permits binocular fusion may, in situations where disparity relationships are abnormal, suppress enough inputs to restore single vision. This possibility is consistent with the pattern of morphological shrinkage since an inability to fuse the inputs from the two eyes would, by definition, not involve the monocular segments.

Infant- and Adult-onset Monocular Paralysis: LGN Morphology

The present data show substantial differences in the patterns of morphological shrinkage after infant- and adult-onset monocular paralysis. In the adults, cells were shrunken only in the binocular segments of the laminae innervated by the paralyzed eye while in kittens, cells throughout the binocular segments of both A and A1 layers whether innervated by the paralyzed or mobile eye were smaller than normal. Since, in both conditions, no effects were seen in the monocular segments innervated by the paralyzed eye, it seems likely that mechanisms sensitive to binocular disruptions are responsible for the control of cell size in both groups of cats. It is not clear, however, whether the same mechanism is involved in both cases. What is clear is that the difference in the response of the visual nervous system to monocular paralysis in these two conditions depends exclusively on the age of the animal when the paralysis begins.

The differences in the patterns of morphological shrinkage with infant- and adult-onset monocular paralysis are intriguing. While it is quite possible that this difference is due to the fact that the mechanisms responsible for the sensitivity of the mature LGN are incompletely developed or absent in the infants, the cellular shrinkage in the laminae innervated by the mobile eye in the animals reared with monocular paralysis seems difficult to explain on this basis. The defects in reflexive movement of the normal eye found in strabismic cats (Cynader & Harris, 1980) could also be present in cats reared with monocular paralysis and could cause the additional morphological effects in the monocular paralyzed kittens by simply making the sensory defect bilateral.

Normal binocular exposure is required for the development of eye alignment in kittens (Blake, Crawford, & Hirsch, 1974; Cynader, 1979; Cynader, Berman, & Hein, 1976; Sherman, 1972). It is not particularly surprising, therefore, that the "normal" eye moves abnormally under certain circumstances. Further, if the movement capabilities of the two eyes are disrupted, it is possible that the immature nervous system cannot discriminate which eye is the source of the disruption. In the adults, the "source eye" can perhaps be identified because of its failure to conform to the "expectations" of the mature nervous system following eye movement commands. These expectations may well develop during infancy with the develoment of eye alignment, and the experience

of predictable change in retinal image with eye movement (Hein, Vital-Durand, Salinger, & Diamond, 1979). Without this experientially generated yardstick, the immature visual system may be incapable of determining that only one eye has been manipulated. It is possible, therefore, that the adult response to monocular paralysis (i.e., shrinkage in binocular portions of laminae innervated by the paralyzed eye) is the "normal" response, and that the symmetric effects of infant-onset monocular paralysis reflect simply the inability of the nervous system to identify which eye is the source of the disruption. This analysis raises the possibilities that binocular paralysis in the adult cat would produce a pattern of effects comparable to that caused by monocular paralysis in infants, and that infant-onset binocular paralysis would have the same effects as monocular paralysis.

Binocular Interactions and the Control of LGN Cell Size

The consequences of monocular deprivation have been attributed to unbalanced binocular competitive interactions. This attribution was made initially because the effects of monocular deprivation are much more pronounced that one would expect based on a knowledge of the effects of binocular deprivation (Movshon & Van Sluyters, 1981). That is, while the effects of binocular deprivation might be due solely to an atrophy of disuse phenomenon, the more severe effects of monocular

deprivation in the layers innervated by the deprived eye must be due to the operation of some additional mechanism.

Sherman and Spear (1982) have proposed two mechanisms which act to control, among other things, the development of LGN cell size: a binocular competitive and a binocular noncompetitive mechanism. These mechanisms were suggested to describe the interactions which can occur between afferents of the two eyes during development. At the simplest level, one can imagine two neurons, one representing each eye (e.g., LGN relay cells), which both innervate the same postsynaptic neuron (e.g., a binocular cortical cell). If the success with which one of the presynaptic cells makes and maintains contacts with the postsynaptic cell is independent of the success of the other presynaptic neuron, a binocular noncompetitive mechanism is said to be operating. Alternatively, if the two presynaptic neurons must vie for a limited number of postsynaptic contact sites, their relative rates of success are dependent, and a binocular competitive mechanism is said to be operating. These concepts were developed by Sherman and Spear (1982) based on (and to account for), among other things: (1) differences in the pattern and magnitude of the morphological effects of monocular deprivation within the LGN, and (2) differences between the patterns and magnitudes of the morphological effects of monocular and binocular deprivation.

With binocular deprivation, the development of LGN cell size is affected in the binocular and monocular segments of the A and A1 laminae in both hemispheres. Since cells in the monocular segment are representing visual field locations served by only one eye, these cells are presumed to be free of any binocular competitive interactions. Cell size reductions in the LGN after binocular deprivation are on the order of roughly 5-10% with no differences between monocular and binocular segments (Guillery, 1973; Hickey, et al., 1977). Because of the comparability of the magnitude of these effects in binocular and monocular segments, and similarity to the size of the effect in the deprived monocular segment after monocular deprivation, these effects were attributed to a noncompetitive binocular mechanism.

With monocular deprivation, cell size is reduced in the LGN laminae innervated by the deprived eye. Unlike binocular deprivation, however, monocular deprivation results in cell size changes which are much more pronounced in the binocular (30-49%) than monocular (about 10%) segment (Sherman & Spear, 1982). The large difference between the sizes of the effects of monocular deprivation in the binocular and monocular segments were taken to imply the operation of a binocular noncompetitive mechanism in the monocular segment and a binocular competitive mechanism (perhaps in combination with the baseline effects of the binocular noncompetitive mechanism) in the binocular segment (Sherman & Spear, 1982). Based on these data, and those from binocularly deprived cats,

it can be surmised that: (1) a binocular competitive mechanism is activated by an asymmetric disruption. This asymmetry is presumably required in order to establish a competitive imbalance. A binocular competitive mechanism should also have greater effects in the binocular, relative to monocular segment. Further, the competitive imbalance should logically result in a laminar pattern of effects where only laminae innervated by the manipulated eye are affected deleteriously resulting in large between layer differences. (2) A binocular noncompetitive mechanism, on the other hand, would be activated by a symmetric disruption which does not present the opportunity for a competitive imbalance. Since no imbalance is present, the monocular and binocular segments should be equally affected, and no between layer differences should exist.

Infant-onset monocular paralysis is an asymmetric visual "deprivation" which results in a pattern of cell size development which is not consistent with the action of either a binocular competitive or binocular noncompetitive mechanism. Since the manipulation seems asymmetric, one would have expected a large shrinkage in the binocular segments of the laminae innervated by the paralyzed eye, and perhaps a smaller cell size reduction in the "deprived" monocular segment. In contrast to these expectations based on the effects of monocular deprivation, infant-onset monocular paralysis produced cell shrinkage which was both smaller (20% versus 30-49%) and distributed differently

than that found with monocular deprivation. The fact that infant-onset monocular paralysis produced shrinkage in the binocular, but not monocular, segment is cinsistent with the operation of a binocular competitive mechanism. The presence of shrinkage in both "deprived" and "nondeprived" laminae, however, is not. In fact, the symmetry of the cell size reductions in both sets of layers is consistent with the operation of a binocular noncompetitive mechanism. The absence of an equivalent effect in the monocular segment, however, is not. Since infant-onset monocular paralysis is an asymmetric deprivation which has symmetric effects which do not involve the monocular segments, it would seem that an additional mechanism may exist for the control of LGN cell size other than the binocular competitive and noncompetitive mechanisms proposed by Sherman and Spear (1982).

Infant-onset monocular paralysis results in a pattern of morphological effects which cannot be accounted for by either the competitive or noncompetitive mechanisms proposed by Sherman and Spear (1982). It is possible, however, that the difference between the effects infant-onset monocular paralysis and monocular deprivation can be explained using a relationship which has been hypothesized to exist between LGN cell body size and the size of geniculocortical axonal arbors (e.g., Movshon & Van Sluyters, 1981). This hypothesis states that geniculate cell body size is determined in part by the size of cortical arbors and the associated increase in the amount of cellular

machinery required to maintain the larger intracellular volume and/or the increased number of geniculocortical synapses (Sherman & Spear, 1982). This hypothesis states that the shrinkage of cells in the deprived laminae after monocular deprivation is due to the fact that their geniculocortical axonal arbors are abnormally small (Shatz & Stryker, 1978) with fewer functional synaptic contacts. a competitive imbalance between the afferents serving the two eyes would, therefore, result in selective shrinkage only in laminae innervated by the deprived eye. If this hypothesis relating LGN cell size to geniculocortical axonal arbor size is true, the symmetric shrinkage after infant-onset monocular paralysis would arise because the geniculocortical afferents serving both eyes are equivalently smaller than normal. Some support for this possibility can be derived from data involving infant-onset strabismus. It is the case that geniculocortical afferents serving the two eyes are more clearly segregated (i.e., are abnormally small) after rearing with strabismus with the terminal fields of both eyes being equally affected (Hubel & Wiesel, 1965). Further, as suggested previously for the data of Ikeda, et al. (1977) and Tremain and Ikeda (1982), the cell shrinkage after strabismus could well be symmetrical. These data would clearly be consistent with the hypothesized relationship between cell body size in the LGN and the size of geniculocortical axonal arbors. This possibility can be tested directly by using histochemical methods to assess the relative sizes of ocular

dominance columns in the striate cortex of cats reared with monocular paralysis.

The idea of symmetrically reduced arbor sizes after infant-onset strabismus suggests that a competitive imbalance between the afferents of the two eyes is not established by this procedure. Similarly, monocular paralysis during infancy may establish a set of circumstances where inputs of the two eyes engage in competition, perhaps because of the mismatch of the two monocular retinal images, but a competition in which neither eye enjoys a clear advantage. The morphological effects of monocular deprivation and strabismus in visual cortex are consistent with the operation of binocular competitive interactions with and without advantage, respectively. In the cortex of monocularly deprived cats, there is a substantial loss of binocularity (Sherman & Spear, 1982) which could simply reflect the reduction in the capacity of the deprived eye inputs to drive any cortical cells. With strabismus in kittens (e.g., Chino, et al., 1983) and monocular paralysis in adults (e.g., Fiorentini, et al., 1979), there is no loss of inputs from either eye to cortex. Rather, there is simply a loss of binocularity. Infant-onset monocular paralysis and monocular deprivation could, therefore, both establish situations where inputs from the two eyes engage in competition. These rearing conditions might differ, however, in that monocular paralysis confers no competitive advantage on either eye while monocular deprivation clearly does. If this analysis is

correct, the differences in the patterns of the morphological effects of infant-onset monocular deprivation and monocular paraysis would reflect the operation of a binocular competitive mechanism with or without one eye enjoying a competitive advantage.

Adult-onset monocular paralysis, on the other hand, results in a pattern of morphological effects which may be consistent with the operation of a binocular competitive mechanism. That is, adult-onset monocular paralysis, like infant-onset monocular deprivation, results in shrinkage only in the binocular segment of the laminae innervated by the "deprived" eye. It must be noted, however, that the amount of shrinkage is much less after adult-onset monocular paralysis (about 17%) than after infant-onset monocular deprivation (30-49% [Sherman & Spear, 1982]). Even though comparisons between these two conditions involve differences in both age of onset and stimulus content of the perturbation, the fact that both situations might be activating the same binocular competitive mechanism prompts speculation. If the similarity between the patterns of the morphological effects of adult-onset monocular paralysis and infant-onset monocular deprivation is of ultimate importance, one must conclude that the operation of the binocular competitive mechanism of Sherman and spear (1982) is not restricted to some period early in life (i.e., the critical period). If this is true, the difference in the magnitudes of shrinkage with these two procedures could reflect simply the reduced vulnerability of the

mature, adult visual system to the operation of the binocular competitive mechanism. On the other hand, if the magnitude of the effect is of importance, and is not related to relative degrees of maturation, the mechanism operating in the adults after monocular paralysis would seemingly differ from that operating in infants after monocular deprivation. This heretofore unidentified mechanism would nonetheless be a binocular competitive mechanism as defined by Sherman and Spear (1982), but a new one. Therefore, whether pattern or size (or both) are of importance in identifying mechanisms controlling LGN cell size,it is clearly the case that consequences of binocular competitive interactions can be found in adult animals. Since the effects of the binocular competitve mechanism are not restricted to visual perturbations occurring within the critical period, one would have to conclude that the binocular competition of Sherman and Spear (1982) is not simply a developmental process. Consequently, the inferences regarding development drawn from the vast body of literature which have used the binocular competitive mechanism associated with monocular deprivation to investigate visual system development may require tempering.

Are Y-cells Lost With Infant-onset Monocular Paralysis?

In monocularly paralyzed cats, changes in physiology have been observed in both laminae A and A1 of the LGN contralateral to the paralyzed eye, whether the paralysis was initiated during infancy or adulthood (Salinger, et al., 1977b, 1978). Certain aspects of those data, however, prompted Salinger, et al. (1978) to hypothesize that the cats reared with monocular paralysis had lost both X- and Y-cells. If one is permitted to assume for the sake of argument that the shrinkage in the cats monocularly paralyzed as adults reflects the loss of X-cells, the present data permit one to inquire as to whether the cats reared with monocular paralysis suffered an additional loss of Y-cells, relative to animals paralyzed as adults, as initially hypothesized by Salinger, et al. (1978). Since the larger cells in the cell body distribution taken from a normal subject are most likely Y-cells (Friedlander, et al., 1979, 1981; Hollander & Vanegas, 1977; LeVay & Ferster, 1977), one can address this question by comparing the relative proportions of large cells in the two groups. If Y-cells are lost in the infant-onset condition, fewer large cells should be present. Further, in order to control for the presumed shared effect on X-cells, it seems reasonable to conduct such a comparison only for those laminar locations in which the adult-onset group differed from normal. When this comparison was made, the cats reared with monocular paralysis were

found to have significantly fewer large cells than cats which underwent monocular paralysis as adults. It would appear, therefore, that the present morphological data support the hypothesis that cats reared with monocular paralysis do suffer a loss of Y-cells in addition to a loss of X-cells shared in common with cats paralyzed as adults.

Further support for this hypothesis can be derived from behavioral data from strabismic cats which suggest that this rearing condition affects both X- and Y-cells (Holopigian & Blake, 1983; Jacobson & Ikeda, 1979). On the other hand, X-cells are selectively suppressed with adult-onset monocular paralysis, and the activity of Y-cells may actually be facilitated (Garraghty, et al., 1982). These hypothesized differences in the effects of infant- and adult-onset monocular paralysis could be tested behaviorally. While reduced spatial acuity would be expected under both circumstances because X-cells seem to be especially involved in spatial vision (Ikeda & Wright, 1972), the animals reared with monocular paralysis would be expected to show additional defects in temporal resolution and resolution for low spatial frequencies, functions for which Y-cells are especially suited (Ikeda & Wright, 1972). Those observations taken together with ones involving animals reared with monocular deprivation (e.g., Sherman & Spear, 1982) or strabismus (e.g., Tremain & Ikeda, 1982) suggest that any visual perturbation beginning during the critical period will affect Y-cells. In addition to this effect, it appears that an additional immediate

change in X-cell properties is found with rearing conditions which require active suppression to relieve diplopia (e.g., monocular paralysis and strabismus).

Infant- and Adult-onset Monocular Paralysis: LGN Physiology

The differences in the physiological consequences of infant- and adult-onset monocular paralysis do not permit one to conclude that different mechanisms are being affected by paralysis in the two contexts. It could be, for example, that the same mechanisms which reduce X-cell encounter rates in adult cats also can affect Y-cells after infant-onset monocular paralysis because of the relative immaturity of Y-cells in infants (Daniels, et al., 1978; Norman, et al., 1977). This could be comparable to the differential effects of visual deprivation in infants and adults. Infant-onset visual deprivation has a profound effect upon LGN Y-cells (Sherman, et al., 1972; Sherman & Spear, 1982), while visual deprivation beginning in adulthood affects X-cells selectively (Salinger, et al., 1977a). Further, long-term infant-onset monocular deprivation does have a delayed impact upon X-cells (Mangel, et al., 1983). In fact, both X- and Y-cells are affected by long-term infant-onset monocular paralysis (Salinger, et al., 1978), monocular deprivation (Lehmkuhle, et al., 1978, 1980, 1982; Mangel, et al., 1983; Mower & Christen, 1982), and

strabismus (Holopigian & Blake, 1983; Ikeda & Tremain, 1979; Jacobson & Ikeda, 1979; Wesson & Loop, 1982). In the final analysis, therefore, similar mechanisms could be operating with each of these perturbations. Age of onset and the relative vulnerability of the cell types would then determine the precise nature of the physiological effect.

The hypothesis originally proposed by Salinger, et al. (1978) to account for the physiological effects of infant-onset monocular paralysis, therefore, may require revision. Salinger, et al. (1978) proposed that X- and Y-cells were lost in the LGN after infant-onset monocular paralysis with the Y-cell loss occurring early and the X-cell loss later in the course of visual system development. This sequence of effects could be comparable to that found in cats reared with monocular deprivation (Mangel, et al., 1983). The loss of spatial resolution of X-cells after infant-onset strabismus, however, occurs early in development (Ikeda, et al., 1977). The nature of the stimulus disruptions may, therefore, determine whether X-cells are lost during or after the critical period. With monocular deprivation, the first indication of X-cell dysfunction is detected at six months of age (Mangel, et al., 1983). On the other hand, the effects of infant-onset strabismus on X-cells can be detected as early as four months of age (Ikeda, et al., 1977), prior to the end of the critical period (Movshon & Van Sluyters, 1981). It seems likely, therefore, that the loss of X-cells in cats reared with monocular paralysis is produced prior to the

end of the critical period, and not later as suggested by Salinger, et al. (1978). Recordings in the LGN of monocularly paralyzed kittens early in life (e.g., prior to the end of the critical period) could resolve the question of the time course of the X-cell loss after infant-onset monocular paralysis.

Infant- and Adult-onset Monocular Paralysis: Other Comparisons

Other consequences of infant- and adult-onset monocular paralysis can be compared if, as appears to be the case, the data from strabismic kittens may be taken as supplemental to and predictive of what would be found with infant-onset monocular paralysis. The visual acuity of the squinted eye has been shown to be dramatically reduced after the induction of infant-onset strabismus (Jacobson & Ikeda, 1979; Von Grunau & Singer, 1980). Further, it appears that the vision of the "normal" eye may be affected as well (Holopigian & Blake, 1983; and see Jacobson & Ikeda, 1979; Von Grunau & Singer, 1980). While no published data exist for cats monocularly paralyzed as adults, unpublished observations for one subject tested in Salinger's laboratory do exist. This one cat showed a pronounced reduction in visual acuity through the paralyzed eye. The postoperative acuity of the mobile eye also showed a very slight (and certainly nonsignificant) reduction in acuity. It could be the case, therefore, that visual acuity is similarly affected

in both conditions. In addition to the effects on acuity, cats reared with strabismus demonstrate a perimetric loss in the nasal visual field of the squinted eye (Ikeda & Jacobson, 1977; Kalil, 1977). That is, the size of the visual field for the deviated eye was found to be reduced with the strabismic cats failing to respond to stimuli introduced into the contralateral nasal field. This same pattern of results has also been obtained in monocularly paralyzed adult cats (Garraghty, Salinger, & MacAvoy, 1978). It could be, therefore, that this aspect of visual function is affected similarly by both infant- and adult-onset monocular paralysis (or strabismus).

The physiological effects of adult-onset monocular paralysis in cortex have been studied (Berman, et al., 1979; Buchtel, et al., 1975; Fiorentini & Maffei, 1974; Fiorentini, et al., 1979; Maffei & Fiorentini, 1976a). A reduction in cortical binocularity was observed in all but one of those reports (i.e., Berman, et al., 1979). While no cortical recording has been performed on cats reared with monocular paralysis, data from cats reared with strabismus have also shown a reduction in the proportions of binocular cells in cortex (Bennett, et al., 1980; Blakemore & Eggers, 1978, 1979; Chino, et al., 1983; Kalil, et al., 1978; Yinon, 1976; Yinon, et al., 1975). To date, the only report which has assessed cortical response parameters other than binocularity in cats reared with strabismus (Chino, et al., 1983) has shown that neurons in cortex tend to have larger receptive fields and

lower spatial and temporal contrast sensitivity than normal. Further, the cortical neurons in these strabismic cats showed these deficiencies whether they were driven principally by the deviated or the normal eye. As mentioned previously, those data agree quite well with the behavioral observations of Holopigian and Blake (1983). It would be most useful to have similar data from monocularly paralyzed adult cats to determine if response features other than binocularity are affected.

What Reflects Amblyopia?

The present data have broad implications for the use of various animal models for the study of the human clinical defect of amblyopia. Those animal models have provided the opportunity to assess the central neurophysiological and anatomical correlates of the visual dysfunction, with the obvious goals of identifying the substrate for the visual defect. Monocular deprivation and strabismus have been used as models for amblyopia (e.g., see Movshon & Van Sluyters, 1981). Do these manipulations have common physiological and/or morphological effects which might reflect functional amblyopia?

LGN physiology. Infant-onset monocular deprivation in cats results in a large loss of Y-cells in the deprived laminae (e.g., Sherman, et al., 1972). If the deprivation is maintained beyond the end of the critical period, a dysfunction in X-cell function (i.e., reduced spatial acuity) emerges at about six months of age (Mangel, et al., 1983). The

reduced spatial acuity of X-cells after infant-onset strabismus, on the other hand, is evident in four month old kittens (e.g., Ikeda, et al., 1977). Further, the observations of Salinger, et al. (1978) strongly suggest that cats reared with monocular paralysis suffer a loss of Y-cells in addition to the loss of X-cells. Since no single laboratory has reported results for more than one of these preparations, it is not possible to determine whether the degree of Y-cell loss and X-cell loss (or dysfunction) are comparable under these various conditions. It would seem possible, therefore, that changes in the function of one or both of these cell classes could be the neural basis for the functional amblyopia which accompanies monocular deprivation or strabismus.

Three observations argue against this possibility. First, infant-onset monocular paralysis results in physiological effects in the contralateral A1 lamina, innervated by the mobile eye (Salinger, et al., 1978) which appear comparable in magnitude to those in lamina A, innervated by the paralyzed eye. The functional defects which follow strabismus, however, are far more pronounced in the squinted eye (Holopigian & Blake, 1983). Secondly, less direct evidence against a loss of LGN cell classes causing amblyopia can be inferred from the observation that geniculate physiology is normal in the deprived laminae of monocularly deprived primates (Irwin, et al., 1983; Sesma, et al., 1982). The deprived eyes of such animals are, nonetheless, amblyopic (e.g., Von Noorden, Dowling, & Ferguson, 1970). A final argument

against the special involvement of X-cell dysfunction in the functional loss of vision is that monocularly deprived kittens are behaviorally amblyopic at five months of age, presumably before the reduction in X-cell spatial sensitivity emerges (Mangel, et al., 1983). It would seem, therefore, that geniculate physiology, at least at the level for which measures exist, is not directly correlated with amblyopia. That is, the functional loss of vision cannot be related directly to a loss or change in function of one or more classes of LGN cells.

LGN morphology. Cell size in the lateral geniculate nucleus might seem, at first glance, to provide an index of amblyopia. Cats reared with monocular deprivation display profound amblyopia in the deprived eye, and a pronounced shrinkage of cells in the deprived geniculate laminae. Monocularly deprived monkeys display this pattern as well (Casagrande & Joseph, 1980; Vital-Durand, et al., 1978; Von Voorden, et al., 1970; Von Noorden & Middleditch, 1975). Data from the cats reared with monocular paralysis, and perhaps strabismic cats (Ikeda, et al., 1977; Tremain & Ikeda, 1982), however, show that cell size is as reduced in geniculate laminae innervated by the "normal" eye as in the laminae innervated by the manipulated eye. While it is possible that the visual capacities of both eyes are affected by strabismus, vision in the deviated eye is substantially worse (Holopigian & Blake, 1983). There is not, therefore, an obvious correlation between the magnitude of cellular shrinkage and the degree of visual impairment.

These observations seemingly leave open the possibility that a correlation between the presence of cellular shrinkage and a functional loss of vision might be present. Data involving dark-reared cats eliminate this possibility as well. As mentioned previously, cell size in the LGN develops normally in dark-reared cats (Kratz, et al., 1979). In cats reared in the dark throughout the presumed critical period, subsequent exposure to monocular deprivation results in a loss of functional deprived eye inputs to cortex, but has no effect on the size of deprived LGN cells or the anatomical size of their cortical arbors (Mower & Caplan, 1983). Nevertheless, there is a loss of vision in the deprived eye (Timney, Mitchell, & Cynader, 1980). It appears, therefore, that while reductions in average cell size in the geniculate may reliably predict a functional loss of vision, the reverse is not necessarily true.

Visual cortex. Rearing a cat with monocular deprivation results in a striate cortex (i.e., area 17) practically devoid of functional input from the deprived eye. Only about 5% of the cells in cortex will respond to stimulation of the deprived eye (e.g., Sherman & Spear, 1982), and the ocular dominance columns serving the deprived eye are physically shrunken (e.g., Shatz & Stryker, 1978). The loss of vision in the deprived eye could, therefore, seemingly be related to a loss of cortical circuitry in area 17. That this is not the case has been shown in two ways. First, there is a loss of binocularity in the cortex of

strabismic cats but there is no ascendency of inputs from the nondeviated eye (Bennett, et al., 1980; Blakemore & Eggers, 1978, 1979; Chino, et al., 1983; Kalil, et al., 1978; Yinon, 1976; Yinon, et al., 1975). The greater loss of acuity in the deviated eye (Holopigian & Blake, 1983), therefore, is not correlated with a relative loss of functional inputs to cortex from the deviated eye. These data suggest that the amount of circuitry in area 17 devoted to processing visual inputs is not related to visual acuity. This conclusion receives support from observations in cats which underwent bilateral ablation of area 17. Visual acuity in these cats was subnormal, but far better than that in the deprived eye of monocularly deprived cats (Berkeley & Sprague, 1979; Lehmkuhle, et al., 1982). Since area 17 apparently contributes very little to visual acuity, it is not surprising that measurements taken there may be unrelated to amblyopia.

It appears, therefore, that the morphological and physiological effects of monocular deprivation, monocular paralysis, and strabismus in the LGN and in area 17 may have little or no predictive relationship to losses of visual acuity characteristic of amblyopia. The absence of obvious neurobehavioral correlations is somewhat discouraging and suggests that more data (especially within-subject correlational data) is needed. While monocular deprivation has been extensively studied, it is not clear that any of its prominent effects in geniculate and striate cortex are causally related to the functional amblyopia. Strabismus and

monocular paralysis, on the other hand, have received relatively little attention, but the data which are available show no obvious causal relationships. It would seem that researchers must consider searching for the neural correlates of amblyopia outside the geniculostriate system. Extrastriate visual cortex offers an obvious place to look. Further, it would be helpful to have more data on behavioral and neural development in the same animals. Between-subject variability could act to obscure neurobehavioral correlations. Tighter correlations would be expected when both neural and behavioral measures are taken in the same animals.

Is Cell Size Related to Physiology in the LGN?

The idea that cell size in the lateral geniculate nucleus is related to electrophysiological encounter rates for the various cell types was derived largely from studies involving monocular and binocular deprivation. Monocular deprivation results in a marked reduction in average cell body size in the binocular segments of the A and A1 layers innervated by the deprived eye. There is also a sizable loss of Y-cells in these same regions. Binocular deprivation, on the other hand, produces reductions in cell body size throughout the monocular and binocular segments of the A and A1 laminae of both hemispheres. Physiologically, there is a corresponding loss of Y-cells throughout the geniculate. There is, therefore, with monocular and binocular

deprivation, a direct correspondence between the sites of morphological and physiological consequences. Further, these effects are correlated in that the degree of cellular shrinkage and the magnitude of Y-cell loss were found to coincide. Monocular deprivation results in a larger degree of shrinkage and a greater loss of Y-cells than does binocular deprivation. These high degrees of correspondence were taken to suggest the existence of a direct (i.e., causal) relationship between these aspects of physiology and morphology.

Dissociations of electrophysiology and morphology in the cat LGN, however, have now been demonstrated under three different sets of circumstances. The first report of such a dissociation was in dark-reared cats. These animals were found to be deficient in Y-cells even though LGN cell size was normal (Kratz, et al., 1979). Further, if cats were reared in the dark for the first four months of life and then brought into a normal visual environment for up to two years thereafter, the physiology of the lost Y-cells never recovered. The second demonstration of a dissociation of this sort was by Geisert, et al. (1982) who reported that cell size returned to normal in the deprived laminae of monocularly deprived cats when the nondeprived eye was enucleated. Y-cell encounter rates, however, remained depressed unless (and until) the deprived eye was also opened. Finally, in the present experiment, adult-onset monocular paralysis which has physiological effects in both the A and A1 laminae in both hemispheres, was found to

produce cell shrinkage only in geniculate laminae innervated by the paralyzed eye. Given the absence of correspondence in these intances, one wonders if some common factor, or set of factors, can be used to predict the presence or absence of a dissociation between geniculate physiology and morphology.

The search for commonalities among the several examples of dissociations between cell size and probability of electrophysiological encounter is, however, predicated on the assumption that under normal circumstances these factors should be related. That is, one could ask whether the covariance of morphology and physiology which has been suggested represents a causal relationship or simply a coincidence. After all, instances of so-called agreement do not outnumber the growing list of examples of dissociation. The data from the dark-reared cats may have already resolved this question in favor of coincidence. Dark-reared cats have normal cell size but are deficient in Y-cells, a situation which is not rectified by subsequent visual experience (Kratz, et al., 1979). Presumably, since the mechanism controlling the growth of geniculate cells does not require visual input while the one controlling the development of Y-cell physiology does, these two mechanisms are different, and seemingly independent. If this is the case, dissociations should be no more surprising than congruencies.

Is LGN Cell Size Related to the Size of Cortical Arbors?

At birth, the geniculocortical afferents arising from the LGN ramify widely in cortex with considerable overlap of the axonal arbors serving the two eyes. With normal binocular experience, these cortical arbors retract somewhat resulting in a segregation of afferents which corresponds directly with the ocular dominance columns (Hubel & Wiesel, 1977; LeVay, et al., 1978). If a cat is reared with monocular deprivation, however, the deprived eye drives very little activity in visual cortex (e.g., Wiesel & Hubel, 1963b), and the geniculocortical afferents arising from the deprived eye actually occupy less cortical territory (e.g., Shatz & Stryker, 1978). Further, the cells in the LGN laminae innervated by the deprived eye are much smaller than normal (e.g., Kalil, 1980). Based on these observations, it has been suggested that LGN cell size is related to the size of the axonal arbors of geniculocortical axons (e.g., see Movshon & Van Sluyters, 1981). As it turns out, the width of cortical ocular dominance columns is well correlated with the relative sizes of cells in different layers of the LGN (Dursteler, Garey, & Movshon, 1976; Garey & Dursteler, 1975; Movshon & Dursteler, 1977; Mower & Kaplan, 1983; Sherman, Guillery, Kaas, & Sanderson, 1974; Vital-Durand, et al., 1978). Furthermore, the time course of geniculate cell size changes and their reversals is comparable to the time course of the effects on cortical binocularity

and size of ocular dominance columns (Cragg, Anker, & Wan, 1976; Dursteler, et al., 1976; Movshon & Dursteler, 1977; Wan & Cragg, 1976). These observations are consistent with the idea that the size of LGN cells is determined by the success with which individual cells make functional contacts with cortical target cells (e.g., see Movshon & Van Sluyters, 1981; Sherman & Spear, 1982). Retrograde effects of this sort have been reported in other neural systems (e.g., Lund, 1978).

The relationship between LGN cell body size and arbor size in cortex may also exist in cats reared with monocular paralysis or strabismus if the previous reassessment of the data of Ikeda and colleagues (Ikeda, et al., 1977; Tremain & Ikeda, 1982) is appropriate. The existence of ocular dominance columns was first noticed in the cortex of cats reared with strabismus (Hubel & Wiesel, 1965). The demonstration of the segregation of ocular inputs was made easier in these cats because the geniculocortical axons serving the two eyes were more clearly separated, presumably reflecting the reduction in binocularity. The sizes of the geniculocortical axonal arbors in these animals were, therefore, probably smaller than normal (e.g., Hubel, et al., 1977). The shrinkage of cells throughout the binocular segment of all LGN laminae after infant-onset monocular paralysis (and possibly strabismus) is consistent with this liklihood. That is, if the geniculocortical axons serving each eye have abnormally small cortical arbors, cell size should be reduced in all geniculate laminae

independently of the status of the innervating eye. It appears, therefore, that LGN cell sizes and the sizes of their arbors in cortex may be related in cats reared with monocular paralysis or strabismus just as in monocularly deprived cats.

Does this relationship between the sizes of geniculate cell bodies and their cortical arbors always exist? In other words, are there examples of a dissociation between LGN cell size and a loss of functional inputs to cortex? If LGN cell size reflects cortical arbor size and cortical arbor size is associated with a loss of functional inputs, it would appear that cats which have undergone monocular paralysis as adults provide evidence for just such a dissociation. That is, since adult-onset monocular paralysis results in shrinkage only in laminae innervated by the paralyzed eye, the paralyzed eye should have less influence in cortex. In other words, since the pattern of shrinkage in the LGN is comparable to that found with monocular deprivation, the "deprived" eye should drive very few cortical cells. Five experiments have studied the effects of adult-onset monocular paralysis in cat cortex (Berman, et al., 1979; Buchtel, et al., 1975; Fiorentini & Maffei, 1974; Fiorentini, et al., 1979; Maffei & Fiorentini, 1976a). A decrease in the relative number of cortical cells driven by the paralyzed eye was not detected in any of these experiments. Therefore, it would appear that the size of cells in the LGN need have no relationship whatsoever to their ability to drive cells

in cortex. These data suggest strongly that the relationship between LGN cell size and arbor extent may be, as is the case with the apparent relationship between cell size and encounter rate, coincidental. There have been no other examples of a dissociation between LGN cell size and cortical responsiveness, but the possibility of a breakdown in this relationship in monocularly paralyzed adul cats suggests that either these two aspects of the visual system may not be causally related, or perhaps that a direct linkage does exist, but only in a developmental context. This question can be directly assessed by measuring the geniculocortical arbors of cats monocularly paralyzed as adults.

What Does LGN Cell Size Reflect?

The instances of dissociations between LGN cell size and electrophysiological encounter rates for the various cell types suggest that the mechanisms which control these aspects of the visual system are independent. These dissociations raise the obvious question as to what changes in cell body size distributions actually reflect. The classic dictum of neuroanatomy is that structure implies function. It would seem, therefore, that if cell sizes are decreased, some functional changes must also be present. However, physiological responsiveness is abnormal in the laminae innervated by the mobile eye of monocularly paralyzed adult cats (Garraghty, et al., 1982) and in all laminae in dark-reared cats (Kratz, et al., 1979), but cell size is normal.

Further, cell size can be reduced in the absence of any detectable change in physiological activity. In monocularly deprived primates, the LGN laminae innervated by the deprived eye contain cells which are smaller, on the average, than normal (Casagrande & Joseph, 1980; Vital-Durand, et al., 1978; Von Noorden & Middleditch, 1975), but which are nevertheless physiologically normal (Irwin, et al., 1983; Sesma, et al., 1982). It would appear, therefore, that functional suppression is neither necessary nor sufficient to produce a reduction in cell size.

Cell size also cannot reliably be a simple reflection of the relative size of geniculocortical axonal arbors. In the present study, average cell size was reduced in laminae innervated by the paralyzed eye in the cats monocularly paralyzed as adults, but previous physiological experiments have given no indication that asymmetric changes in the sizes of functional geniculocortical arbors are present (Berman, et al., 1979; Buchtel, et al., 1975; Fiorentini & Maffei, 1974; Fiorentini, et al., 1979; Maffei & Fiorentini, 1976a). Therefore, while reductions in the size of a cell's cortical arbor might reliably predict a shrinkage of its soma, the reverse is not necessarily true. The existence of these kinds of conditional relationships between structure and function more likely reflect an ignorance of the relevant physiological parameter(s) than a true dissociation of morphology from physiology. It is not clear at this time, however, what other functional changes might be related to cell size reductions. Perhaps a

considerably more detailed assessment of the physiological effects of monocular paralysis in the adult cats (e.g., deoxyglucose assessment of metabolic activity [Sokoloff, Reivich, Kennedy, DeRosiers, Pattak, Pettigrew, Sakurada, & Shinohara, 1977]) will reveal interocular differences which might account for the anatomical changes. In any case, while the attempts which have been made to correlate a variety of physiological and morphological measures (e.g., Y-cell encounter rates and average LGN cell size) have been of great heuristic value, they may have suffered from the common tendency to reify correlation to suggest causation.

Genetic and Environmental Influences on LGN Cell Growth and Size

Results from the present experiment together with other observations in the literature suggest that nature and nurture play different roles in different aspects of visual system development. Cell size in the LGN proceeds normally in the absence of visual inputs of any kind (Kratz, et al., 1979). On the other hand, similar rearing conditions permanently reduce the encounter rate for Y-cells but have no detectable effect on geniculate X-cells (Kratz, et al., 1979). Therefore, some aspects of visual system development (e.g., LGN cell size) are apparently under rather strict genetic control, requiring no visual inputs for either the initiation of the critical period or their

subsequent development. While this genetic control exists, it may be superceded by environmental factors. For example, abnormal rearing procedures can affect cell size. Other aspects of visual system development (e.g., Y-cell physiological development), on the other hand, require visual inputs, and those inputs must be available during initial postnatal development.

The different responses of the infant and adult visual system to monocular paralysis clearly demonstrate some sort of critical or sensitive period phenomenon. That is, the response of the immature brain to monocular paralysis must, at some point, give way to the mature, adult response. That thenervous system responds differentially to identical sensory disturbances beginning at different times during development is in itself not surprising. In rats, for example, maternal malnutrition during fetal development, or infant malnutrition during the first 21 postnatal days prevents the brain from growing at its normal rate (Winick, 1976). Part of this effect is due to a decrease in cell size, but cell size is also reduced if malnutrition occurs much later in life, and cell size can be increased with improved nutrition (Winick, 1976). The crucial distinction between early and late malnutrition is that early postnatal and prenatal malnutrition reduces the actual number of cells that are eventually created by about 15% (Winick, 1976), and later improvement in nutrition does not restore these deficits. This loss of cells is presumably due to the timing of the malnutrition with

respect to the time-course of cell genesis during development. These findings raise an important ditinction regarding the etiology of effects of sensory disturbances (or any teratogenic influence). Some consequences of a sensory defect might be function-related while others are purely developmental (i.e., growth dependent processes). For example, it is very possible that Y-cells are lost after visual deprivation in kitten because their development is peaking when the deprivation begins whereas X-cells are already relatively mature (Irwin, et al., 1983; Sesma, et al., 1982), rather than because of any special sensitivity. This possibility receives strong support from the findings of Salinger, et al. (1977a) that deprivation in adult cats affects X- and not Y-cells. Similarly, the infant response to monocular paralysis may involve Y-cells in addition to the X-cell loss shared with adults (Salinger, et al., 1978) simply because of their relative immaturity and not because of their sensitivity to the sensory modifications which stem from monocular paralysis. There has been no hint of a deleterious effect on LGN Y-cells in adults after monocular paralysis (Garraghty, et al., 1982) even though the sensory disturbance is identical to that in the infants.

Finally, it must be emphasized that the effects of infant-onset monocular paralysis are not simply growth-related responses to a visual perturbation in a generic sense. The response of the infant LGN to monocular paralysis involves both X- and Y-cells and morphological

shrinkage in the A and A1 laminae in both hemispheres. Infant-onset monocular deprivation, on the other hand, affects principally Y-cells and results in cellular shrinkage only in laminae innervated by the deprived eye. It would seem, therefore, that at least some part of the effects of monocular paralysis in the infants is related to the nature of the stimulus disruption, and not merely the age of the cat at the time the sensory modification is introduced.

CHAPTER V

SUMMARY

Single unit recording of cells in the lateral geniculate nucleus (LGN) of cats have shown that monocular paralysis results in changes in the physiology of the nucleus. In adult cats, this change in physiology has been characterized as a reduction in the relative encounter rate for X-cells. In cats reared with monocular paralysis, on the other hand, both X- and Y-cells are apparently lost. The present study has measured the sizes of LGN cells after infant- and adult-onset monocular paralysis in an attempt to assess whether correlated morphological changes also occur. Cell body size measurements were also made in the LGNs of normally-reared adult cats for purposes of comparison. In all subjects, data were collected in portions of the binocular segments of the A and A1 laminae representing 0-5°, 6-20°, and 21-45°. Data were also collected in the monocular segment. One hundred cell were measured in the seven zones in each LGN, for a total of 1400 in each subject.

The data collected in the normal adult cats constitute the first assessment of changes in average cell body size as a function of horizontal eccentricity within the normal ...iculate. It had been suggested previously that average cell size tends to increase with increasing eccentricity. This seemed a reasonable suggestion since

Y-cells are larger than X-cells and become proportionately more plentiful at greater eccentricities. The present data, however, have shown that cells in the portions of the LGN representing retinal or visual eccentricities in excess of 20° are significantly smaller than more centrally located cells. Therefore, if a size gradient exists in the LGN, cells tend to become smaller with increases in eccentricity. These data further indicate that absolute size values cannot be used to separate X- from Y-cells throughout the LGN, as has been suggested. Rather, one or both of these cell classes must become smaller in geniculate locations serving the peripheral visual field. Support for the proposition that Y-cells become smaller with increases in eccentricity can be derived from the fact that of the geniculate regions sampled in the present study, average cell size was smallest in the monocular segment even though Y-cells account for a much larger proportion of the population in that region. This observation is in agreement with other reports in the literature of cell size in the monocular segment.

Cell measurements in the cats which underwent monocular paralysis as adults showed that average cell size was reduced in virtually all of the binocular segments of the LGN laminae A and A1 innervated by the paralyzed eye. These data constitute yet another manifestation of adult neural plasticity. These observations, together with previous electrophysiological experiments in the LGN and visual cortex of

monocularly paralyzed adult cats, demonstrate two kinds of dissociation of morphology and physiology. First, the physiological loss of X-cells in the LGN after monocular paralysis is present in the A and A1 laminae of both hemispheres. The loss of X-cells in the layers innervated by the mobile eye is, therefore, not associated with a corresponding reduction in average cell body size. Secondly, LGN cell size has been hypothesized to be related to the size of geniculocortical axonal arbors in cortex. It is very unlikely that arbor sizes have been reduced in these subjects, so the cell size reductions must reflect something else. Finally, the data from these adult cats demonstrate that binocular mechanisms previously thought to operate only during development may also be present and usable in the mature visual system.

In the cats reared with monocular paralysis, cell size reductions were found in the A and A1 laminae of both hemispheres, whether the innervating eye was paralyzed or mobile. In contrast to the adults, this pattern of morphological change seems to be consistent with both the pattern of electrophysiological changes in the LGN and the probable symmetric reductions in anatomical arbor size of the geniculocortical afferents serving the two eyes. Since monocular deprivation results in cellular shrinkage only in laminae innervated by the deprived eye, it is possible that the effects of infant-onset monocular paralysis reflect the operation of a mechanism which has not been previously described. The effects of infant-onset monocular deprivation have been ascribed to

binocular competition with the nondeprived eye enjoying a competitive advantage. This competitive imbalance is manifested as a selective shrinkage of cells in the LGN laminae innervated by the disadvantaged, deprived eye. In contrast, the morphological effects of infant-onset monocular paralysis were found to be symmetrically distributed in the LGN regardless of whether the innervation was provided by the paralyzed eye or not. This could seemingly reflect the operation of a binocular competitive mechanism in which the inputs from neither eye were at an advantage (i.e., both eyes were equally disadvantaged). This kind of binocular competition has not been previously described.

The different morphological effects of infant- and adult-onset monocular paralysis are apparently related to differences in age at the time the perturbation is introduced. It is not clear, however, whether different mechanisms are responsible for the effects in these two conditions, or the same mechanism is operating differentially due to maturational influences. The fact that LGN laminae are affected after infant-onset monocular paralysis whether they are innervated by the paralyzed or mobile eye while only laminae innervated by the paralyzed eye are affected by adult-onset monocular paralysis raises the possibility that the immature visual system cannot discriminate which eye has been immobilized whereas the adult, mature system can.

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Appendix A: Protocol for processing tissue with cresyl violet.

1.	70% Ethyl alcohol in distilled water (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 (depending upon age of stain)	30 sec.-2 min.
13.	Distilled Water	Rinse
14.	70% ETOH	Differentiate gray matter
15.	90%	Clear white matter
16.	100% ETOH	Rinse
17.	100%	5 min.
18.	Xylenes	5 min.
19.	Coverslip	

Appendix B: Individual subject data for the five normally reared adult cats. These data are collapsed across hemispheres, so that 200 observations contributed to the relative frequency distributions for each eccentricity bin in each layer of each subject.

0-5°

Lamina A

Upper Limit (μm^2)	04	08	10	12	13
100	1.0	1.5	2.0	2.0	0.0
150	12.5	11.5	14.0	17.5	9.0
200	31.5	24.0	19.5	31.0	34.0
250	26.5	28.5	26.5	21.5	29.5
300	10.0	16.5	14.0	16.5	13.5
350	10.0	10.0	9.5	5.0	6.5
400	4.5	5.0	5.5	2.5	3.5
450	2.0	1.0	2.5	2.0	2.0
500	1.5	1.0	4.5	1.0	2.0
550	0.5	0.0	0.0	1.0	
600		0.5	1.0		
650		0.5	0.0		
700			1.0		

Lamina A1

100	1.5	0.5	0.5	1.0	0.0
150	12.0	13.0	13.0	14.0	4.5
200	25.0	19.0	17.5	37.5	20.5
250	33.5	20.0	24.0	27.5	32.0
300	13.5	17.5	20.0	9.0	18.0
350	7.0	13.0	11.5	5.5	10.0
400	2.0	7.0	5.5	2.5	7.5
450	1.5	3.5	3.5	2.5	3.0
500	2.0	2.0	2.5	0.5	2.0
550	0.5	1.5	0.5		1.5
600	1.5	1.0	1.0		0.5
650		0.5	0.0		0.0
700		1.0	0.0		0.0
750		0.0	0.5		0.5
800		0.5			

6-20°

Lamina A

Upper Limit (μm^2)	04	08	10	12	13
100	0.0	0.5	6.0	0.5	0.0
150	3.5	9.0	15.0	13.5	9.0
200	16.0	29.0	27.0	33.5	27.0
250	34.5	26.0	18.5	28.0	23.5
300	20.5	16.5	13.5	9.0	12.5
350	8.5	8.5	8.5	8.0	11.5
400	7.0	4.0	4.5	4.5	7.5
450	2.5	3.0	1.5	1.0	3.0
500	3.0	1.0	3.0	1.0	3.5
550	2.0	1.0	1.0	0.5	1.5
600	1.0	1.0	0.5	0.5	1.0
650	1.0	0.5	1.0		
700	0.0				
750	0.0				
800	0.5				

Lamina A1

100	0.0	1.5	2.5	0.0	0.5
150	2.5	13.0	11.0	12.5	8.5
200	20.5	21.0	15.5	35.0	24.0
250	30.5	29.0	18.5	21.5	28.0
300	15.5	17.0	14.5	16.0	17.0
350	11.0	7.0	10.5	9.5	7.5
400	9.5	4.5	9.5	4.0	6.0
450	2.0	3.5	6.0	1.0	4.0
500	2.5	2.0	4.5	0.0	2.0
550	3.0	1.0	4.0	0.0	2.0
600	2.0	0.5	2.5	0.5	0.0
650	1.0		0.5		0.5
700			0.5		

Upper Limit (μm^2)	21-45° Lamina A				
	04	08	10	12	13
100	2.0	2.0	3.5	4.5	3.0
150	14.0	17.0	16.5	25.0	14.0
200	25.0	31.5	26.0	36.0	28.5
250	27.5	27.5	24.0	18.5	27.0
300	13.5	13.5	13.0	8.5	14.5
350	8.0	5.0	6.5	6.0	6.0
400	5.0	1.5	6.0	1.5	4.0
450	3.0	0.5	2.0		2.0
500	1.5	0.5	2.0		1.0
550	0.5	0.0	0.5		
600		1.0			
			Lamina A1		
100	1.5	1.5	1.5	3.5	1.0
150	15.0	9.5	10.5	25.5	17.0
200	28.0	35.0	22.5	29.0	25.5
250	27.0	25.0	23.0	20.5	24.5
300	12.0	15.5	19.5	9.5	15.0
350	7.5	6.5	8.5	3.5	9.5
400	3.0	4.5	5.5	7.0	4.0
450	3.5	1.0	3.0	1.0	2.0
500	1.5	0.0	2.5	0.5	1.0
550	0.5	1.0	1.0		0.0
600	0.0	0.0	0.5		0.5
650	0.5	0.0	1.5		
700		0.5	0.5		

Upper Limit (μm^2)	Monocular Segment				
	04	08	10	12	13
100	0.0	7.5	5.0	0.0	9.5
150	3.0	38.0	21.0	20.0	27.0
200	23.0	27.5	23.5	45.0	27.5
250	33.0	20.5	27.0	21.0	21.5
300	17.5	5.0	9.5	9.0	10.0
350	14.0	1.5	8.5	4.5	2.5
400	4.0		3.5	0.5	1.0
450	4.0		0.5		1.0
500	1.0		0.5		
550	0.5		0.5		
600			0.5		

Appendix C: Individual subject data for the four cats which underwent a prolonged period of monocular paralysis beginning in adulthood. Each relative frequency distribution is based on 100 observations. Left and right refer to hemisphere. In all cases, the left eye was paralyzed. Therefore, left lamina A1 and right lamina A were innervated by the paralyzed eye.

0-5°

Lamina A

Upper Limit (μm^2)	Left				Right			
	01	03	07	09	01	03	07	09
100	6.0	0.0	1.0	3.0	1.0	5.0	4.0	1.0
150	20.0	6.0	8.0	17.0	21.0	28.0	25.0	28.0
200	37.0	14.0	26.0	32.0	41.0	30.0	37.0	32.0
250	16.0	22.0	21.0	24.0	16.0	20.0	18.0	22.0
300	12.0	28.0	19.0	16.0	6.0	10.0	7.0	10.0
350	4.0	16.0	14.0	2.0	8.0	2.0	6.0	3.0
400	2.0	8.0	5.0	3.0	5.0	2.0	0.0	1.0
450	1.0	1.0	1.0	1.0	2.0	1.0	0.0	0.0
500	2.0	2.0	2.0	1.0		0.0	3.0	2.0
550		0.0	2.0	0.0		0.0		1.0
600		1.0	0.0	1.0		2.0		
650		2.0	0.0					
700			1.0					

Lamina A1

100	3.0	3.0	3.0	1.0	2.0	0.0	3.0	6.0
150	15.0	20.0	22.0	18.0	16.0	5.0	14.0	30.0
200	28.0	30.0	33.0	28.0	33.0	14.0	20.0	32.0
250	29.0	20.0	24.0	24.0	32.0	29.0	27.0	16.0
300	12.0	16.0	11.0	17.0	6.0	17.0	21.0	9.0
350	3.0	4.0	4.0	4.0	7.0	10.0	4.0	4.0
400	4.0	2.0	2.0	2.0	0.0	8.0	2.0	2.0
450	3.0	3.0	1.0	1.0	1.0	5.0	5.0	1.0
500	0.0	1.0		4.0	1.0	7.0	1.0	
550	2.0	0.0		1.0	1.0	3.0	3.0	
600	0.0	1.0			1.0	2.0		
650	1.0							

6-20°

Lamina A

Upper Limit (μm^2)	Left				Right			
	01	03	07	09	01	03	07	09
100	0.0	3.0	1.0	9.0	3.0	8.0	10.0	1.0
150	2.0	11.0	19.0	33.0	33.0	30.0	33.0	20.0
200	13.0	23.0	43.0	30.0	32.0	35.0	36.0	40.0
250	32.0	21.0	23.0	13.0	16.0	21.0	10.0	16.0
300	17.0	20.0	7.0	4.0	5.0	1.0	8.0	13.0
350	12.0	8.0	5.0	3.0	9.0	5.0	2.0	6.0
400	9.0	5.0	0.0	1.0	2.0		1.0	2.0
450	7.0	2.0	1.0	4.0				0.0
500	4.0	1.0	1.0	3.0				0.0
550	2.0	1.0						0.0
600	2.0	2.0						2.0
650		1.0						
700		0.0						
750		2.0						

Lamina A1

100	7.0	1.0	0.0	0.0	3.0	2.0	3.0	4.0
150	21.0	11.0	10.0	4.0	25.0	13.0	25.0	25.0
200	26.0	27.0	24.0	15.0	16.0	30.0	25.0	27.0
250	22.0	27.0	23.0	29.0	17.0	24.0	24.0	20.0
300	9.0	17.0	11.0	20.0	7.0	14.0	12.0	12.0
350	8.0	6.0	13.0	8.0	12.0	8.0	6.0	8.0
400	3.0	1.0	6.0	12.0	6.0	2.0	0.0	1.0
450	3.0	4.0	6.0	5.0	6.0	3.0	1.0	2.0
500	1.0	2.0	4.0	3.0	4.0	2.0	2.0	0.0
550		0.0	2.0	1.0	3.0	2.0	1.0	0.0
600		1.0	0.0	2.0	1.0		1.0	1.0
650		2.0	0.0	0.0				
700		1.0	1.0	0.0				
750				1.0				

21-45°

Lamina A

Upper Limit (μm^2)	Left				Right			
	01	03	07	09	01	03	07	09
100	2.0	1.0	11.0	6.0	3.0	3.0	14.0	13.0
150	16.0	22.0	41.0	27.0	29.0	17.0	53.0	48.0
200	30.0	39.0	30.0	31.0	34.0	39.0	17.0	19.0
250	16.0	23.0	10.0	18.0	19.0	19.0	10.0	10.0
300	17.0	5.0	4.0	8.0	6.0	10.0	3.0	2.0
350	14.0	4.0	3.0	6.0	5.0	8.0	1.0	5.0
400	4.0	3.0	0.0	2.0	2.0	1.0	2.0	1.0
450	1.0	3.0	0.0	0.0	2.0	2.0		2.0
500			1.0	1.0		1.0		
550				1.0				

Lamina A1

100	0.0	0.0	3.0	4.0	0.0	3.0	5.0	5.0
150	6.0	8.0	28.0	24.0	9.0	16.0	25.0	30.0
200	25.0	34.0	34.0	39.0	22.0	16.0	34.0	26.0
250	14.0	29.0	18.0	13.0	27.0	22.0	15.0	18.0
300	23.0	20.0	8.0	10.0	16.0	19.0	12.0	6.0
350	14.0	4.0	2.0	5.0	10.0	11.0	2.0	5.0
400	7.0	3.0	4.0	1.0	8.0	4.0	2.0	5.0
450	4.0	0.0	3.0	0.0	1.0	2.0	3.0	1.0
500	4.0	1.0		3.0	5.0	6.0	2.0	2.0
550	2.0	1.0		1.0	1.0	0.0		2.0
600	1.0				0.0	1.0		
650					1.0			

Upper Limit (μm^2)	Monocular Segment							
	Left				Right			
	01	03	07	09	01	03	07	09
100	6.0	2.0	11.0	17.0	2.0	13.0	22.0	10.0
150	27.0	28.0	49.0	37.0	19.0	38.0	44.0	39.0
200	26.0	41.0	30.0	27.0	35.0	31.0	18.0	33.0
250	22.0	21.0	7.0	9.0	19.0	9.0	11.0	15.0
300	8.0	6.0	0.0	8.0	16.0	6.0	3.0	2.0
350	7.0	2.0	3.0	2.0	6.0	3.0	2.0	1.0
400	2.0				3.0			
450	0.0							
500	2.0							

Appendix D: Individual subject data for the four cats reared with monocular paralysis. Each relative frequency distribution is based on 100 observations. Left and right refer to hemisphere. In all subjects, the left eye was paralyzed. Therefore, left lamina A1 and right lamina A were innervated by the paralyzed eye.

0-5°

Lamina A

Upper Limit (μm^2)	Left				Right			
	02	05	06	11	02	05	06	11
100	2.0	9.0	8.0	0.0	10.0	21.0	6.0	3.0
150	23.0	26.0	35.0	16.0	19.0	50.0	22.0	18.0
200	35.0	30.0	36.0	40.0	42.0	16.0	42.0	34.0
250	23.0	21.0	15.0	26.0	20.0	11.0	21.0	25.0
300	11.0	8.0	3.0	12.0	3.0	2.0	7.0	10.0
350	3.0	4.0	3.0	6.0	5.0		1.0	5.0
400	1.0	0.0			1.0		1.0	4.0
450	1.0	1.0						1.0
500	1.0	1.0						

Lamina A1

100	2.0	7.0	16.0	2.0	5.0	4.0	10.0	1.0
150	12.0	28.0	35.0	9.0	25.0	48.0	34.0	31.0
200	36.0	27.0	37.0	29.0	33.0	27.0	44.0	39.0
250	33.0	19.0	9.0	38.0	19.0	11.0	10.0	18.0
300	14.0	14.0	3.0	11.0	13.0	7.0	2.0	4.0
350	2.0	3.0		3.0	3.0	2.0		5.0
400	0.0	0.0		4.0	2.0	1.0		2.0
450	1.0	2.0		4.0				

6-20°

Upper Limit (μm^2)	Left				Right			
	02	05	06	11	02	05	06	11
Lamina A								
100	0.0	12.0	0.0	0.0	0.0	6.0	0.0	0.0
150	14.0	32.0	3.0	20.0	9.0	49.0	14.0	6.0
200	43.0	32.0	42.0	37.0	40.0	27.0	51.0	31.0
250	19.0	10.0	32.0	24.0	27.0	10.0	22.0	36.0
300	13.0	7.0	9.0	11.0	13.0	6.0	5.0	11.0
350	4.0	4.0	6.0	6.0	5.0	2.0	5.0	11.0
400	5.0	1.0	7.0	0.0	2.0		2.0	2.0
450	2.0	1.0	0.0	2.0	2.0		1.0	2.0
500		1.0	1.0		2.0			0.0
550								0.0
600								1.0
Lamina A1								
100	0.0	12.0	0.0	0.0	0.0	6.0	0.0	0.0
150	4.0	29.0	4.0	10.0	2.0	40.0	6.0	8.0
200	37.0	35.0	48.0	42.0	32.0	36.0	31.0	39.0
250	23.0	15.0	30.0	24.0	25.0	14.0	32.0	20.0
300	19.0	6.0	11.0	15.0	22.0	3.0	20.0	15.0
350	8.0	3.0	7.0	4.0	6.0	0.0	4.0	8.0
400	2.0			2.0	5.0	1.0	6.0	6.0
450	3.0			2.0	5.0		0.0	3.0
500	3.0			1.0	3.0		1.0	1.0
550	1.0							

21-45°

Upper Limit (μm^2)	Left				Right			
	02	05	06	11	02	05	06	11
				Lamina A				
100	2.0	13.0	9.0	4.0	5.0	14.0	11.0	3.0
150	19.0	38.0	39.0	37.0	25.0	61.0	46.0	30.0
200	33.0	33.0	38.0	29.0	30.0	18.0	28.0	44.0
250	24.0	12.0	7.0	20.0	24.0	5.0	10.0	11.0
300	9.0	3.0	6.0	7.0	9.0	2.0	4.0	7.0
350	9.0	1.0	1.0	2.0	5.0		1.0	5.0
400	3.0			0.0	1.0			
450	1.0			1.0	1.0			
				Lamina A1				
100	1.0	11.0	9.0	4.0	0.0	15.0	14.0	0.0
150	23.0	28.0	32.0	21.0	14.0	48.0	42.0	34.0
200	31.0	36.0	42.0	36.0	32.0	21.0	33.0	32.0
250	19.0	15.0	12.0	17.0	26.0	12.0	6.0	21.0
300	13.0	9.0	4.0	17.0	16.0	3.0	5.0	6.0
350	6.0	1.0	1.0	4.0	9.0	0.0		3.0
400	5.0			1.0	1.0	1.0		4.0
450	1.0				2.0			
500	0.0							
550	1.0							

Upper Limit (μm^2)	Monocular Segment							
	Left				Right			
	02	05	06	11	02	05	06	11
100	1.0	2.0	0.0	0.0	0.0	15.0	0.0	0.0
150	14.0	30.0	8.0	16.0	10.0	55.0	13.0	9.0
200	42.0	41.0	36.0	56.0	45.0	23.0	42.0	56.0
250	30.0	17.0	41.0	18.0	24.0	7.0	20.0	28.0
300	9.0	9.0	11.0	4.0	14.0		17.0	5.0
350	3.0	0.0	3.0	3.0	3.0		3.0	1.0
400	1.0	0.0	1.0	3.0	2.0		3.0	1.0
450		1.0			2.0		0.0	
500							2.0	