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The effect of cerebellar and collicular lesions on the relative encounter rates for X and Y cells in the lateral geniculate nucleus of the monocularly paralyzed cat

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THE EFFECT OF CEREBELLAR AND COLLICULAR LESIONS ON THE RELATIVE ENCOUNTER RATES FOR X AND Y CELLS IN THE LATERAL GENICULATE NUCLEUS OF THE MONOCULARLY PARALYZED CAT

by

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Several converging lines of evidence suggest that the integration of binocular visual with binocular proprioceptive information takes place in the lateral geniculate nucleus (LGN) and it is very likely that such integration is necessary for normal binocular vision and depth perception. A naturally occurring visual anomaly, strabismic amblyopia, which results in the lack of normal stereoscopic vision and reduction of visual acuity, may be the outcome of a perturbation of these integrative mechanisms. Monocular paralysis, an experimental manipulation which, in part, serves to mimic some aspects of strabismic amblyopia, has been shown to disrupt binocular-visual/proprioceptive integrative mechanisms and so may serve as a model for some aspects of amblyopia. Monocular paralysis results in a highly reliable decrease in the encounter rate for X cells relative to Y cells in the LGN six days postoperative.

Questions about the nature of this effect of monocular paralysis which may yield clues about the etiology of strabismic amblyopia and binocular-visual/ proprioceptive mechanisms and their plasticity may be answered, in part, by an analysis of the neural circuitry which supports the maintenance of the monocular paralysis effect. Therefore, it was the purpose of this study to test the hypothesis that the superior colliculus and cerebellum, which receive binocular-visual/proprioceptive information and have direct or indirect input to the LGN, are involved in the maintenance of the monocular paralysis effect. Standard extracellular recording techniques and a battery of tests were used to determine the relative encounter rates for X and Y cells in the LGN to confirm the X cell encounter rate shift subsequent to monocular paralysis and then, after the lesion, again to determine if the X cell encounter rate remained the same or had been restored to higher levels by the lesion. Electrolytic lesions of the

colliculus in areas retinotopically matched to the LGN recording penetrations had no effect on the relative encounter rates for X and Y cells while lesions of the cerebellum increased the encounter rates for X cells in each of four cats tested. An analysis of the cerebellar lesion cites revealed that this increase in the encounter rate for X cells relative to Y cells was not a result of accidental intrusion of the lesion into the brainstem and control experiments showed it could not be attributed to surgical trauma or residual surgical anesthesia. It was suggested that the cerebellum is involved in the integration of binocular-visual/proprioceptive information and may be the source of X cell suppression which during development may result in strabismic amblyopia.

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TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF FIGURES

Page

Figure

CHAPTER I

INTRODUCTION

Binocular Integration in the Lateral Geniculate Nucleus

How the brain creates a cyclopean view from the separate images provided by the two eyes is a problem that has long been a concern of vision research. For anatomical reasons, in the mammalian visual system the first opportunity for this visual integration to take place is the lateral geniculate nucleus (LGN) of the thalamus. Even though the various laminae of the LGN are monocularly innervated, the binocular registration of the laminae (Sanderson, 1971) and massive input from binocular cells in layer VI of visual cortex (Ahlsen, Grant, & Lindstrom, 1982; Geisert, Langsetmo, & Spear, 1981; Gilbert & Kelly, 1975; Guillery, 1967; Harvey, 1978; 1980; Hollander, 1970; 1972; Kalil & Chase, 1970; Robson, 1984; Toyama, Matsunami, Ohno, 1969; Tsumoto, Creutzfeldt, Legendy, 1978; Tsumoto & Suda, 1980; Updike, 1975; 1977; Widen & Marsan, 1960) are consistent with a binocular integration function for this "relay" nucleus.

Complementing this view of the LGN as involved with binocular integration, new evidence suggests that mechanisms integrating binocular visual and binocular proprioceptive information may be revealed by changes in the LGN that take place as a result of monocular paralysis. Furthermore, characteristics of the effects of monocular paralysis, discussed in later sections, have broad implications for strabismic amblyopia and visual neural plasticity.

Physiological evidence that the LGN is involved in binocular integration comes from studies which demonstrate the effects on individual cells of the LGN of stimulating the "non-dominant" eye. Each of the laminae of the LGN are

innervated and therefore dominated by primary visual afferents from one or the other eye (Garey & Powell, 1962; Guillery, 1970; Hayhow, 1958; Kaas, Guillery, & Allman, 1972; Laties & Sprague, 1966; Stone & Hansen, 1966). In keeping with this very straightforward anatomical organization is the classic finding that LGN cells respond to visual input from a limited portion of the visual field and are only obviously responsive to stimulation from the "dominant" eye. However, with the application of quantitative techniques to the study of LGN neurons, effects of non-dominant eye stimulation have been well documented (Guido & Spear, in press; Pape & Eysel, 1986; Rodieck & Dreher, 1979; Sanderson, Bishop, & Darian-Smith, 1971; Schmielau & Singer, 1977; Singer, 1970; Varela & Singer, 1987; Vastola, 1960). Visual information from one eye can affect the response of a particular LGN neuron to stimulation by the other eye and thus it appears that some form of binocular integration can begin to occur at the level of the LGN.

If the visual system is to maintain this integration of the separate images provided by the two eyes in an active, behaving organism, it would seem to require information about the relative position of the two eyes in order to correctly interpret the disparities between the two images provided by the eyes. There is a massive research literature which supports the idea that this information is at least partially supplied to the central nervous system by stretch receptors located in the extraocular muscles. This "inflow" idea, first suggested by Sherrington (1918), is supported by data that suggests that not only are subjects aware of inflow information about eye position, but can use this information to control eye position in the dark (Skavenski, 1971; 1972; Skavenski & Steinman, 1970). Steinbach and Smith (1981) found that strabismics pointed (without sight of the hand) to targets after corrective surgery with accuracy that could not be accounted for by "outflow" theory (Helmholtz, 1910/1962). These results confirm the suspicion that

proprioception must be used to control gaze since people who have been blind in one eye from birth still have apparently perfectly conjugate eye movements as adults (Steinbach, 1987). (It should also be noted that there is evidence that outflow information, derived from motor commands directing gaze, is also available as a cue for eye movements [Guthrie, Porter, Sparks, 1983; Matin, Picoult, Stevens, Edwards, Young, MacArthur, 1982].)

The finding that humans use inflow information to facilitate visually guided behavior has been extended in the animal literature. Binocular integration (as measured by the proportion of binocularly responsive cells in visual cortex) is reduced in kittens which have been deprived of extraocular muscle proprioception (Maffei, 1979), a preparation that has also been shown to produce impaired binocular depth perception in kittens (Graves, Trotter, & Fregnac, 1984). In adult cats, removal of proprioceptive afferents leads to impairment of visually guided jumping performance (Fiorentini, Berardi, & Maffei, 1982) and depth perception (Fiorentini, Maffei, Cenni, & Tacchi, 1985). These results suggest that integration of extraocular muscle proprioceptive information with visual information is important for normal binocular vision and depth perception and for their development. This integration of binocular visual with binocular proprioceptive information (binocular-visual/proprioceptive integration) could start to take place as early as the LGN where passive movement of one eye has been found to influence the visual responses of relay cells visually dominated by either eye (Donaldson & Dixon, 1980; Lal & Friedlander, 1986; 1987; 1989).

To summarize, the integration of binocular visual with binocular proprioceptive information takes place in the LGN and it is very likely that such integration is necessary for normal binocular vision and depth perception (Guido, Salinger, & Schroeder, 1988). One way of looking at this process by which central visual structures integrate relative eye position information and

visual information is to look at perturbations of the system (Berkley, 1981; Blake, 1981). It is in this context that we shall discuss the possibility that a naturally occurring visual anomaly, strabismic amblyopia, is the outcome of such a perturbation. Monocular paralysis, an experimental manipulation which, in part, serves to mimic aspects of strabismic amblyopia, will also be examined as a way of studying binocular-visual/proprioceptive integration in the LGN.

In addition, the study of the integration of binocular visual with binocular proprioceptive information may provide models of neural plasticity because this integrative process must accommodate subtle changes, produced by growth, in the interocular distance and size of the eyes. These changes require that the precise algorithm (or at least values of variables in the equation) by which binocular-visual/proprioceptive integration occurs must change as the organism grows (see Blakemore, 1979; Timney, 1984). If neural plasticity is involved in modifying visual integration in the developing organism, then perhaps aspects of the ability of the visual system to respond to changes that take place during maturation have some function and are retained in the adult. For example, retinal disparity provides us with a powerful cue with which to judge depth. How the brain interprets the spatial phase relationships between inputs from corresponding and non-corresponding points on the retina in terms of depth, however, must take into account the fact that these phase relationships depend on the distance between the two eyes and thus must take into account the fact that this distance changes as the organism grows. However, whenever fixation is maintained on a particular object as the head is turned the phase relationships between the inputs from the two eyes also change (as does the relative spatial frequency of the images focused on the retinae) without any obvious distortion of depth perception. This must mean that the system that calculates depth from retinal disparity can take into account moment to moment changes in the rotation of the eyes (both with respect to each other and with

respect to the object) just as it did long-term changes in interocular distance, perhaps through proprioceptive information relayed from the extraocular muscles.

That some sorts of plasticity are characteristic of the adult nervous system is suggested by various demonstrations of relatively stable changes in anatomy and/or physiology that can be induced by changes in patterns of stimulation (e.g., long-term potentiation [see McNaughton, 1983]; learning and memory [Woody, 1986]). The effect of monocular paralysis on the relative encounter rates of X and Y cells in the adult LGN (Brown & Salinger, 1975) confirms that plasticity is also characteristic of the adult visual system. The fact that this monocular paralysis effect is itself the outcome of binocular-visual/proprioceptive integrative mechanisms (Garraghty, Salinger, MacAvoy, Schroeder, & Guido, 1982; Guido et al., 1988) then suggests that neural plasticity is involved in maintaining such mechanisms. Therefore, in the following sections amblyopia and neural plasticity will be discussed in terms of binocular-visual/proprioceptive mechanisms. As these mechanisms are also involved in monocular paralysis, the relationship between monocular paralysis, amblyopia, and neural plasticity will be discussed as well.

Strabismic Amblyopia

General characteristics. Amblyopia, which literally means "dullness of vision" (from the Greek amblyos- dull; opia, from the stem ops- vision), is a condition which afflicts 2-2.5% of the population and is defined as a decrease of visual acuity in one or both eyes which on physical examination appear normal (von Noorden, 1985). Amblyopia can arise as a result of a number of different conditions which result in different types of amblyopias. Since these differences are relevant to the effort being made to model strabismic amblyopia and to understanding the physiological mechanisms underlying the amblyopias we shall first describe the characteristics of the various amblyopias as they have

been observed in humans. Next, a discussion of the models of strabismic amblyopia will suggest that monocular paralysis may mimic some aspects of strabismic amblyopia that other models fail to demonstrate.

There seem to be two basic types of clinical conditions that are known to cause amblyopia: some form of "occlusion" and strabismus, a chronic misalignment of the visual axes of the two eyes. Occlusion amblyopias, which result from a decrease or blurring of visual input may either be unilateral or bilateral. Unilateral occlusion amblyopia may be caused by anisometropia (unequal refraction of the two eyes) or, rarely, visual deprivation (resulting from patching, cataracts, opaque cornea, etc.). Bilateral occlusion amblyopia may result from cataracts of equal density, high, uncorrected hypermetropia (far-sightedness), or motor type nystagmus (von Noorden, 1985).

Strabismus often occurs in conjunction with amblyopia, but the direction of causality is still debated. Early-onset strabismus almost always results in a loss of stereopsis, the perception of the relative distance of two objects from an observer based solely on the slightly disparate views provided by the two eyes (Fox, 1981). However the associated amblyopia seems to be contingent upon whether or not the patient fixates with either eye in an alternating fashion. If the patient is an alternating fixater then monocular properties of the eyes are normal (except, perhaps, for esotropes [see Day, Orel-Bixler, & Norcia, 1987]), but under binocular viewing conditions there is a suppression (Holopigian, Blake, & Greenwald, 1988; Smith, Levi, Manny, Harwerth, White, 1985) of the deviated eye. Regardless of which eye is currently used for fixation, the area of deepest suppression is most intense in a region corresponding to the fovea of the fixating eye (the nasal retina of esotropes and the temporal retina of exotropes), decreasing toward the periphery, and absent in the opposite hemifield (Sireteanu, 1982).

If the patient prefers to fixate only with one eye (usually the non-deviating eye) then an amblyopia of the deviating eye is observed (von Noorden, 1985). In esotropes the loss of visual acuity may be present even in the supposedly "good" eye (Day et al., 1987; Sebris & Dobson, 1987). This amblyopia, unlike anisometropic amblyopia which may affect the entire binocular visual field, is only present in the central 20° (affecting the nasal retina, of esotropes, more severely) while the remainder of the visual field remains relatively unaffected (Hess & Pointer, 1985; Sireteanu & Fronius, 1981; but see Bradley, Freeman, & Applegate, 1985).

Binocular summation and interocular transfer of adaptation after-effects, very much reduced in the central region of the visual field of strabismic amblyopes, are highly significant in the periphery (Sireteanu, Fronius, & Singer, 1981). In anisometropic amblyopes both binocular summation and interocular transfer of adaptation after-effects are lost at all tested eccentricities (Sireteanu et al., 1981).

Aside from its associated amblyopia, strabismus itself is a complex condition resulting in visual confusion, diplopia, possible defocus of the deviating eye, and perhaps abnormal patterns of oculomotor feedback, so it is not obvious which of these visual perturbations actually causes amblyopia in strabismics (Boothe, Dobson, & Teller, 1985). Certainly strabismic amblyopia is a condition which seems to exhibit the characteristics of a situation in which visual integrative processes have broken down. Therefore, it is important to understand the precise antecedent condition (i.e., the precipitating factor) of amblyopia in strabismus if we are not only to improve our general understanding of this condition, but also to understand if and how the integration of binocular visual with binocular proprioceptive information is involved in strabismic amblyopia. Strabismic amblyopia is a reasonable target of experiments whose goal it is to study these processes, but the underlying defects in visual processing in

strabismic amblyopia have been difficult to study because of the inadequacy of the visual models used to explore these defects (Jampolsky, 1978; Marg, 1982). Therefore, a brief discussion of the models of strabismic amblyopia follows.

Deprivation models of strabismic amblyopia. The most prominent effect in strabismic amblyopia, aside from the loss of stereopsis, is a loss of acuity in the deviated eye (von Noorden, 1985). This suggests a reduction in the spatial frequency resolution or loss of X cells since these cells are probably responsible for our perception of fine detail (Lehmkule, Kratz, Mangel, & Sherman, 1980; Lennie, 1980; Sestokas & Lehmkuhle, 1986). However, the surgical preparation receiving the most attention as an animal model of amblyopia, infant onset monocular deprivation, results in a loss of Y cells rather than of X cells (Friedlander, Stanford, & Sherman, 1982; Sherman, Hoffmann, & Stone, 1972; Sherman & Spear, 1982) suggesting it is not a good model for strabismic amblyopia. An infant onset binocular deprivation model also is at variance with the characteristics of strabismic amblyopia not only because Y cell loss is its prominent feature but because the loss occurs preferentially over the peripheral rather than central LGN representations of binocular visual space (Sherman et al., 1972). As noted above, in strabismic amblyopia, losses are typically limited to central visual space (Hess, 1982; Hess, Campbell & Zimmern, 1980; Hess & Pointer, 1985; Sireteanu & Fronius, 1981; but see Bradley et al., 1985). In summary, preparations involving deprivation of visual stimulus to one or both eyes seem to be inadequate for modeling relevant aspects of strabismic amblyopia.

Experimental squint as a model of strabismic amblyopia. Transection of the lateral rectus muscle results in a lasting esotropia in cats and monkeys, that, if accomplished during infancy results in amblyopia. Similar surgery at later ages in cats results in strabismus, but not amblyopia (Jacobson & Ikeda, 1979). This

parallels well with the common observation that adult onset strabismus does not result in amblyopia (von Noorden, 1985).

Physiologically, cats raised with strabismus seem to demonstrate effects that would be expected given the data on perceptual losses suffered by human strabismic amblyopes. Certainly the most dramatic effect of early onset strabismus is the lack of binocularly responsive cells in visual cortex (Crawford & von Noorden, 1979; Hubel & Wiesel, 1965; Van Sluyters & Levitt, 1980; Xue, Freeman, Carney, & Shadlen, 1987). It has also been found that the spatial resolving power of cortical neurons is reduced (Chino, Shansky, Jankowski, & Banser, 1983).

The reduced spatial resolution of cortical neurons may be secondary to geniculate losses. Recordings of LGNs of esotropic cats reveals that X cells driven through the nasal retina (mostly near the fovea) of the deviating eye had spatial resolutions lower than normal (Ikeda, Plant, & Tremain, 1977; Ikeda & Wright, 1976; Jones, Kalil, & Spear, 1984). This finding mirrors nicely the fact that spatial resolution losses in human esotropes is mainly in the deviating eye in the region of the visual field corresponding to the nasal retina and are most intense in central visual space (Sireteanu & Fronius, 1981). Physiological findings of nasal field losses are also supported by morphological studies which show that LGN cells with inputs from the deviated eye are smaller than normal and that the effect on cells size is greatest in the region of the LGN corresponding to the nasal field of the deviated eye (Ikeda et al., 1977; Tremain & Ikeda, 1982).

The aberrant physiology of the LGN and cortex of strabismic cats may, in part, derive from retinal abnormalities. Ikeda and Tremain (1979) found that in those strabismic cats which always fixated with the non-deviating eye X cells in the area centralis of the deviating eye show lower than normal spatial resolution. This finding was later confirmed (Chino, Shansky, Hamasaki, 1980)

but has also been challenged (Cleland, Crewther, Crewther, & Mitchell, 1982). Differences in results may reflect different surgical procedures, with only a more radical surgery (Ikeda & Tremain, 1979) resulting in retinal abnormalities (Crewther, Crewther, & Cleland, 1985) or, perhaps, age at which the surgery is performed (Crewther, Crewther, & Cleland, 1985).

Unfortunately, it is very difficult to obtain information about the perceptual information about the visual acuity of different parts of the visual field in cats so direct confirmation of perceptual losses in human amblyopes is not available. However, it has been found that cats raised with strabismus are less responsive to stimuli presented in the nasal field of the deviating eye when tested monocularly (Ikeda & Jacobson, 1977; Kalil, 1977; Sireteanu & Singer, 1984). In addition, the visual acuity and contrast sensitivity of the deviating eye in cats raised with strabismus is impaired (Jacobson & Ikeda, 1979; Holopigian & Blake, 1983; Cleland et al., 1982; Holopigian & Blake, 1984) like that of humans (Bradley et al., 1985; Day et al., 1987; Hess & Bradley, 1980; Hess et al., 1980; Hess & Pointer, 1985; Mathews, Yager, Ciuffreda, & Richter, 1984; Sebris & Dobson, 1987; Sireteanu & Fronius, 1981; Smith et al., 1985). Therefore, behavioral data suggest that strabismus in cats is a reasonable model of human strabismic amblyopia.

In summary, in many ways the surgical transection of the lateral rectus muscle of kittens during the first few weeks after birth produces effects in the adult that resemble some aspects of human strabismic amblyopia.

Monocular paralysis as a model of strabismic amblyopia. Aspects of the effects of monocular paralysis may make this preparation a better model in some respects than those used in the past (monocular deprivation) because of the similarities between it and certain features of strabismic amblyopia which are not seen in other preparations (Guido, 1984). Monocular paralysis is accomplished by the surgical transection of cranial nerves III, IV, and VI which

provide innervation to the extrinsic and intrinsic muscles of the eye. Single unit recording of the LGN contralateral to the paralyzed eye 14 days post-operative has revealed that the encounter rate for X cells is significantly lower relative to the encounter rate detected 1 to 3 days post-operative (Brown & Salinger, 1975).

There are several ways in which strabismic amblyopia and monocular paralysis are similar. First, and most obviously, both result in misaligned visual axes which diminishes the ability to achieve alignment. Secondly, strabismus involves amblyopia in the deviated eye which seems to be confined mostly to central visual space (Hess, 1982; Hess et al., 1980; Sireteanu, 1982; Sireteanu & Fronius, 1981). Although acuity deficits have not been investigated in monocularly paralyzed animals the X cell suppression that is found in the LGN is also limited to areas representing central visual space (Garraghty et al., 1982). Since it has been suggested that the X cell pathway mediates high spatial resolution (Lehmkule et al., 1980; Lennie, 1980; Sestokas & Lehmkuhle, 1986) this agrees well with the central visual space deficits of strabismic amblyopes. Third, strabismic amblyopia seems to involve a process which is centrally mediated, and not retinal in origin (Hess, 1982; Hess, Campbell, & Greenhalgh, 1978; Sireteanu, 1982; Jampolsky, 1978). Similarly, monocular paralysis seems to be the function of a centrally mediated process which is sensitive to chronic ocular misalignment (Garraghty et al., 1982; Guido et al., 1988; Schroeder, Salinger, & Guido, 1988). The extrinsic component of monocular paralysis has been mimicked using tenotomization and results in an X cell encounter rate shift similar to that of monocular paralysis (Salinger, Garraghty, MacAvoy, & Hooker, 1980). The intrinsic component, mimicked by daily application of atropine, results in continuous dilation of the pupil and loss of accommodation in one eye but does not result in an X cell encounter rate shift (Salinger et al., 1980). These results indicate that it is the misalignment

of the eyes and not the chronically defocused image that resulted in the suppressed X cell encounter rate. Fourth, strabismic amblyopia can be partially reversed by ocular realignment (Scott, 1983). It has also been shown that the effects of monocular paralysis can be reversed by eliminating sensory input (extraocular proprioception and visual input from the non-paralyzed eye) that convey the fact of the misalignment of the eyes (Guido et al., 1988). Fifth, strabismic amblyopia is characterized in part by the lack of stereoacuity in patients (von Noorden, 1985) thus suggesting that very few binocular visual cortical cells are present. Likewise, it has been shown that the number of binocular cells present in the visual cortex of monocularly paralyzed cats is reduced (Maffei & Fiorentini, 1976; Fiorentini, Maffei, & Bisti, 1979).

Even though monocular paralysis seems to mimic certain aspects of strabismic amblyopia certain other features of monocular paralysis demand skepticism. Most importantly, the effects of monocular paralysis (X cell suppression), unlike those of strabismic amblyopia (Jacobson & Ikeda, 1979) can be induced in adults. Strabismic amblyopia, unlike the effect of monocular paralysis, is considered to be a strictly developmental phenomenon (Boothe, 1980; von Noorden, 1985). Further, the visual acuity losses of amblyopia probably result from a decreased spatial frequency resolution of individual X cells in the LGN (Ikeda et al., 1977; Ikeda & Wright, 1976; Jones et al., 1984) rather than a suppression of X cells as in monocular paralysis (Schroeder et al., 1988).

However, X cell suppression can not be ruled out in strabismic amblyopia since most of the work done on the infant onset squint has used only anesthetized conditions and the suppression of X cells after monocular paralysis is only noted under sedated conditions. In fact, there is evidence that the amblyopia of the deviated eye in monkeys and humans may improve after enucleation of the non-deviating eye (Harwerth, Smith, Duncan, Crawford, von

Noorden, 1986; Rabin, 1984; Vareecken & Brabant, 1984). A similar, but much more rapid, recovery has been noted in the deprived eye of cats after enucleation of the non-deprived eye (Smith, 1981a,b; but see Jones, Berkley, Spear, Tong, 1978). This immediate improvement of the visual capabilities of an amblyopic eye may be caused by the release of X cells from suppression which is contingent on the presence of the non-amblyopic eye. The fact that the suppression of X cells in the monocularly paralyzed adult cat can be reversed by removal of visual or proprioceptive input from the normal eye is not only support for this hypothesis, but further links monocular paralysis and strabismic amblyopia.

Taken together, these comparisons between strabismic amblyopia and monocular paralysis suggest that monocular paralysis does not model the amblyopia that results from strabismus. It is clear, however, that changes that occur in the LGN and cortex as a result of monocular paralysis do resemble some aspects of strabismic amblyopia, but what could be the relationship between these two phenomena?

It may be the case that rather than modeling the amblyopia that results from strabismus, that adult monocular paralysis models conditions of suppression in the adult that result in amblyopia if present during infancy. This speculation is suggested by the often-cited idea that long-term chronic suppression is actually responsible for the development of amblyopia in one eye. Indeed, it has been found that portions of the visual field that exhibit deeper interocular suppression also have poorer monocular acuity and areas less strongly suppressed have better acuity (Sireteanu, 1982; Sireteanu & Fronius, 1981).

The mechanism of this suppression evidenced by strabismics is unknown, but there is evidence that it is different from that of binocular rivalry (Holopigian et al., 1988; Smith et al., 1985). The time periods over which

binocular rivalry (seconds) and monocular paralysis (days) suppressive mechanisms operate are completely different, suggesting that these mechanisms are different. Therefore, the finding that the binocular rivalry suppressive mechanism is not involved in strabismic amblyopia does not rule out a role for suppression in the etiology of strabismic amblyopia and is consistent with the idea that the suppressive mechanism evident in monocular paralysis reflects an adult manifestation of this amblyopiogenic suppression.

Summary. In summary, since the study of the breakdown of a system often reveals some aspects of the nature of the intact system a study of strabismic amblyopia may yield clues about the operation of binocular-visual/proprioceptive mechanisms. However, the outcomes of some experimental perturbations of the developing visual system (e.g., monocular deprivation) seem to bear little resemblance to strabismic amblyopia. Monocular paralysis may provide a more useful model for the study of strabismic amblyopia or at least suppressive mechanisms, perhaps initiated by strabismus, which may cause amblyopia. Indeed, the similarity between monocular paralysis and key features of strabismic amblyopia may be indicative of the fact that they reflect the operation of the same integrative mechanisms. Thus, the study of monocular paralysis could be important if we are to understand these mechanisms thought to involve binocular-visual/proprioceptive integration.

Neural Plasticity in the Visual System

Most of the research on the plasticity of the visual system has been devoted to the study of various forms of visual deprivation and their effect on the developing organism. Wiesel and Hubel (1963; 1965; Hubel & Wiesel, 1970) were the first to show changes in the response properties of visual cortical neurons after infant-onset monocular or binocular visual deprivation. Plasticity was subsequently demonstrated in the LGN as well (for review see Sherman &

Spear, 1982). Below, aspects of neural plasticity of the visual system will be discussed that indicate that the effects of monocular paralysis of adult cats may involve mechanisms similar to those of developmental plasticity and may thus be considered a form of neural plasticity.

The fact that changes occur in the visual system in response to manipulation of sensory input is interesting from the physiological standpoint of how the deprivation caused the change. A knowledge of what sorts of perturbations affect the visual system gives us clues not only to what the mechanism of the visual anomaly is, but also of how that mechanism might contribute to the normal development and function of the organism. There are two basic mechanisms that have been postulated to account for deviance from the normal physiology of the visual system (Sherman & Spear, 1982): 1) competitive mechanisms, implying active and perhaps reversible processes and 2) deprivation (of all sensory input; of all sensory input, but at a particular time in development thus only affecting elements experiencing the fastest rate of development; or of specific sensory information to which only a subset of neural elements is sensitive). Deprivation implies a non-active mechanism in which an atrophy of a particular pathway occurs from disuse and is therefore irreversible. In the context of monocular paralysis only the active mechanisms are relevant since it is not a developmental phenomenon (though it has already been speculated that mechanisms similar to those invoked by monocular paralysis may impact development, thus resulting in strabismic amblyopia) and because it is immediately and completely reversible. Evidence that the effects of deprivation in developing organisms also involve, at least in part, active competitive physiological processes has been provided by several lines of research showing: 1) that some of the effects are at least partially and immediately reversible and 2) that the effects of deprivation can be prevented by pharmacological manipulations.

Evidence that the effects of visual deprivation during development are partially reversible comes from work in the LGN and visual cortex. First, Y cell function in the LGN, diminished by early onset monocular or binocular deprivation, can be partially restored by combined opening of the deprived eye and suturing of the nondeprived eye (Hoffmann & Hollander, 1978). It would seem from this study that the Y cells were being actively suppressed rather than simply degenerating. In visual cortex the dominance of the nondeprived eye as the functional input to cortical cells, altered by monocular deprivation, can also be partially reversed by enucleation of the nondeprived eye and opening the deprived eye (Kratz, Spear, & Smith, 1976). This effect can also be achieved by the intravenous administration of bicuculline which blocks the action of gamma-amino-butyric acid (GABA), a putative inhibitory neurotransmitter (Duffy, Snodgrass, Burchfiel, & Conway, 1976) further demonstrating that the inhibition of the input from one eye is an active process (but see Sillito, Kemp, & Blakemore, 1981).

The changes that take place in visual cortex as a result of monocular deprivation can also be prevented by pharmacological manipulations. Intracortical perfusion of the catecholaminergic neurotoxin 6-hydroxydopamine, which can be used to deplete norepinephrine in the brain, protects the normal binocularity of cortex from the effects of monocular deprivation (Gordon, Moran, Trombley, & Soyke, 1986; Kasamatsu & Pettigrew, 1976; see also Kasamatsu, 1983). In addition, the re-introduction of norepinephrine by intracortical perfusion restores the capacity of the visual system to silence inputs from the deprived eye (Kasamatsu & Pettigrew, 1979; Kasamatsu, Pettigrew, & Ary, 1979; Pettigrew & Kasamatsu, 1978; but see Bear & Daniels, 1983; Bear, Paradiso, Schwartz, Nelson, Carnes, Daniels, 1983; Bear & Singer, 1986; Sillito, 1983).

From the above evidence it is clear that neural plasticity characterizes the developing organism, but the functional implications of neural plasticity for the adult organism are not clear. There is, nonetheless, some evidence of neural plasticity in adults. For example, it has been demonstrated that over the course one to two weeks changes in the gain and even the polarity of the vestibulo-ocular reflex can occur in adult subjects as a result of wearing dove prism goggles which reverse left right relations in the visual field (Ito, 1984). Changes in the function of visual cortical neurons are observable after a period (about 7 days) of monocular paralysis (Buchtel, Berlucchi, & Mascetti, 1975; Fiorentini & Maffei, 1974; Fiorentini et al., 1979; Maffei & Fiorentini, 1976).

In addition to changes in visual cortex, as noted above, changes in the LGN of the adult monocularly paralyzed cat have also been noted (Brown & Salinger, 1975). There are at least two indications that the change in the X cell encounter rate of the monocularly paralyzed cat is the result of neural plasticity. First, the suppressed X cell encounter rate does not manifest itself immediately following surgery (Brown & Salinger, 1975). Instead, the effect requires a period of approximately six days post-operative to occur (unpublished observations). Secondly, the critical period for cortical plasticity can be manipulated by introduction of 6-hydroxydopamine. Similarly, the suppression of X cells in monocularly paralyzed cats can be prevented by the application of 6-hydroxydopamine (Guido, Salinger, & Schroeder, 1982) thus suggesting the manipulation of another, perhaps related, plasticity. Third, the effects of monocular paralysis, like monocular deprivation, can be reversed by manipulations of the normal eye (Guido et al., 1988).

Therefore, in addition to monocular paralysis preparation being suitable for the study of binocular-visual/proprioceptive integration in the LGN, this preparation may also provide insight into aspects of adult neural plasticity.

Indeed, it is perhaps the case that this binocular-visual/proprioceptive integration is intimately related to such plasticity.

The Monocular Paralysis Effect as an Indication of Binocular-Visual/ Proprioceptive Integrative Mechanisms

Not only may monocular paralysis model aspects of strabismic amblyopia and adult neural plasticity, but it may also model aspects of normal binocular-visual/proprioceptive mechanisms. As stated above, monocular paralysis results in a relative decrease in the encounter rate for X cells. This "shift" in the X cell encounter rate occurs at eccentricities ranging from 0 to 20° in layers A and C (responsive to the contralateral eye) and 0 to 5° in A1 (responsive to the ipsilateral eye) in the LGN ipsilateral and contralateral to the paralyzed eye (Garraghty et al., 1982).

This finding is important for two reasons. First, the LGN is a bilaterally symmetric structure, with one in each hemisphere (each LGN responds to the contralateral visual hemifield) organized in laminar fashion such that all of the cells in a particular layer receive retinal input from only one eye. Thus we have the apparent paradox of surgical manipulation of one eye affecting LGN neurons that are directly responsive only to the intact eye. Secondly, this manipulation has an effect on the relative encounter rates of X and Y cells in the LGN. The X-Y classification scheme, first described by Enroth-Cugell and Robson (1966), differentiates retinal ganglion cells as well as LGN cells on the basis of their receptive field properties. These two classes of cells may represent fundamentally different ways of processing visual information (Ikeda & Wright, 1972; Sestokas & Lehmkule, 1986) and understanding processes (such as those involved in monocular paralysis) that differentially affect their activity may yield evidence about the nature of these different processes and their possible roles in binocularity. Therefore, a series of experiments was initiated to elucidate which component(s) of monocular paralysis is/are

necessary for manifestation of the effect. The identification of these components firsthand confirmed the binocular-visual/proprioceptive nature of monocular paralysis.

Since monocular paralysis immobilizes extrinsic and intrinsic muscles of the eye, it was unclear which of these components was resulting in the X cell encounter rate shift. The extrinsic component of monocular paralysis has been mimicked using tenotomization and results in an X cell encounter rate shift similar to that of monocular paralysis (Salinger et al., 1980). The intrinsic component, mimicked by daily application of atropine, results in continuous dilation of the pupil and loss of accommodation in one eye but does not result in an X cell encounter rate shift (Salinger et al., 1980). It appears, then, that paralysis of the extrinsic oculomotor muscles of the eye produces the monocular paralysis effect and not paralysis of the intrinsic muscles.

Further analysis reveals that paralysis of the extrinsic muscles and tenotomization produce two classes of effects: 1) abnormal patterns of retinal disparity and visually mediated feedback of ocular motility (retinally mediated) and 2) abnormal patterns of proprioceptive feedback (extraretinally mediated). In an attempt to determine which or if both of these classes of stimuli is important in producing an X cell loss in the LGN, monocular paralysis surgery was performed on cats with concurrent binocular lid suture (to rule out retinally mediated stimuli). Some portions of the X cell loss found in monocular paralysis were unaffected by lid suture. This suggests that the monocular paralysis effect is mediated by retinal and proprioceptive cues and that these components can be separated using appropriate manipulations. Another test of the relevant cues operating in monocular paralysis is the complement of the above study in which either retinal or non-retinal cues were separately removed by denervation after monocular paralysis (Guido et al., 1988). It was found that removing proprioceptive cues by section of nerve V

innervating the mobile eye in a chronic monocularly paralyzed animal resulted in a return of the X cell encounter rate to the level found in the acute preparation in all principle layers of the LGN. Section of nerve V innervating the paralyzed eye had no effect, presumably because the LGN is not responsive to static extraocular muscle signals (Donaldson & Dixon, 1980).

However, as earlier work (Salinger, Garraghty, & Schwartz, 1980) had suggested, retinal cues seem to be important as well. Guido et al. (1988) found that section of the optic nerve of the mobile eye also caused a return to an acute-like X cell encounter rate. This shift was transient, however, lasting only 20 hours in layers A and C and could only be assessed for the first 5 hours in A1 because of nerve degeneration effects which would confound further recording. This result certainly demonstrates that both retinally mediated and extraretinally mediated processes operate in producing the effects of monocular paralysis.

Summary

Since direct visual input to LGN neurons is monocular, the fact that a variety of surgical manipulations of one eye (removal of its oculomotor innervation and, subsequent to this monocular paralysis, removal of visual and proprioceptive afferents of the other eye) affects the X cell encounter rates of the layers of the LGN responding to both eyes indicates that the monocular paralysis effect depends on a binocular process. Therefore, since the LGN receives both proprioceptive and visual information and the maintenance of the monocular paralysis effect relies on both types of information, the LGN is, as suggested in preceding sections, involved not only in binocular visual integration, but also binocular-visual/proprioceptive integration.

The involvement of the LGN in the monocular paralysis effect and its sensitivity to visual and proprioceptive stimulation do not indicate that it is the only central structure involved in these integrative functions. Other structures

receive (and possibly integrate) proprioceptive and visual information and may influence geniculate processing to produce the monocular paralysis effect. In addition, since the monocular paralysis effect is at least related to neural plasticity, structures which are involved in the monocular paralysis effect are perhaps also involved in neural plasticity and permit adaptation of binocular visual and binocular proprioceptive processes to changes in visual stimulation. Another possibility is that these structures do not integrate the sensory information, but are part of the circuitry by which the LGN receives the information necessary for integration. What follows, then, is a brief review of the literature concerning the pathways by which the LGN may come to receive the binocular visual and proprioceptive inputs so that we may recognized those structures which have the highest probability of contributing to the monocular paralysis effect.

Primary Proprioceptive Pathways

The extraocular muscles of the cat are known to contain intramuscular stretch receptors (Cooper & Fillenz, 1955; Corbin & Harrison, 1940). These receptors have been shown to be responsive to muscle stretch in a number of studies, but the location of the cell bodies of these afferents has been of some debate. Both Alvardo-Mallart, Batini, Buisseret, Gueritaud, & Horchelle-Bossavit (1975), using injection of HRP into extraocular muscles, and Fillenz (1955), recording electrophysiological responses to eye muscle stretch, found evidence for extraocular muscle proprioceptive cell bodies in the mesencephalic nucleus. However, other investigators using these same methodologies have rejected these findings and have, instead, supported the hypothesis that the cell bodies of these first order neurons lie in the semilunar (i.e., trigeminal or Gasserian) ganglion (Cody, Lee, & Taylor, 1972; Corbin & Harrison, 1940; Jerge, 1963; Manni, Palmieri, & Marini, 1972a; Porter & Spencer, 1982). In addition, Cody et al. (1972) supported their arguments against mesencephalic involvement

with observations that HRP could diffuse into jaw muscles passing near the eye, thus mimicking a positive result in the mesencephalic nucleus. Further, Jerge (1963) argued that stretch of extraocular muscles causes a disturbance of jaw muscles (leading to physiological responses) due to the incomplete bony orbit of the cat.

Several studies of the lamb and monkey extraocular muscle proprioceptive system support the notion that the second order neurons lie within the trigeminal nucleus (Manni, Palmieri, & Marini, 1971; 1972a; 1972b; 1974; Porter, 1986). However, the central projections from the trigeminal nucleus carrying extraocular muscle signals have not been thoroughly investigated. Manni et al. (1974) found that by physiologically isolating and then destroying extraocular muscle stretch-responsive cells in the nucleus oralis (a subdivision of the trigeminal nucleus) that degenerating fibers terminated ipsilaterally in the medial and lateral aspects of the nucleus ventralis posterior of the thalamus (via the medial lemniscus and the dorsal trigeminothalmic tract). Trigeminothalmic projections have also been studied using retrograde HRP (Burton & Craig, 1979; Matsushita, Ikeda, & Okado, 1982) and retrograde degeneration (Torvik, 1957). They found that the ventral division of the principal trigeminal nucleus (apparently not studied by Manni et al., 1974) projected to the contralateral nucleus ventralis posterior and that the dorsal division projected ipsilaterally to the same nucleus. Since there is a somatotopic arrangement in the trigeminal nucleus in the dorso-ventral direction (Marini & Bortolami, 1979), the contralateral and ipsilateral projections to the thalamus might be meaningful with regard to direction of eye movements. However, this relationship is not obvious since, for example, the lateral and medial recti proprioceptors project ventrally in the trigeminal nucleus and both are therefore represented contralaterally. In summary, there is evidence for proprioceptive input to the thalamus, though it is currently incomplete.

Proprioceptive Input to the LGN and Perigeniculate Nucleus

The central proprioceptive pathways from the trigeminal nucleus to the lateral geniculate complex have not been completely determined, but data from the muscle stretch response properties of LGN neurons (Donaldson & Dixon, 1980) do yield some clues. The wide latency range to eye muscle stretch (5-300 msec) indicates there is probably more than one pathway and at least one is fairly direct. Responses to muscle stretch in the perigeniculate part of the reticular nucleus were found to be similar to those in the LGN. The latencies were slightly longer (9-120 msec) indicating this structure is probably not proprioceptively presynaptic to the LGN. The LGN does not receive a direct input from the trigeminal nucleus or the nucleus ventralis posterior (Hughes & Mullikin, 1984), but it is conceivable that another, yet unnamed nucleus in the thalamus connects the LGN with the trigeminothalamic pathway. It is also possible that the mesencephalic reticular formation, the activity of which has been shown to influence the activity of neurons in the LGN (Sherman & Koch, 1986) and also receives afferent eye movement signals (Cooper, Daniel, & Whitteridge, 1955) may be one source of proprioceptive information to the LGN. Longer latency pathways may involve the cortex, which is itself responsive to extraocular muscle proprioception (Ashton, Boddy, & Donaldson, 1984; Buisseret & Maffei, 1977) and sends corticofugal fibers to the LGN (Updike, 1975; 1977). Pathways to the LGN, such as those involving the superior colliculus and cerebellum, may also contribute longer latency proprioceptive input.

Superior Colliculus

Only the deep layers of the superior colliculus receive direct trigeminal inputs from the contralateral principal nucleus and pars oralis (Baleydier & Mauguiere, 1978; Edwards, Ginsburgh, Henkel, Stein, 1979). Physiological evidence for this direct trigeminotectal pathway for extraocular muscle

proprioception is lacking, but it is known that single units within all layers of the superior colliculus are responsive to passive eye movement with a latency range of 7-108 msec (Rose & Abrahams, 1975). Donaldson and Long (1980) found the same range of responses in the superficial layers of the superior colliculus (5-90 msec), but the distribution is definitely bimodal suggesting two pathways of proprioceptive input to the superior colliculus.

The connectivity of the trigeminotectal pathway does not explain the fact that most of the proprioceptively responsive units in the above study could be stimulated by both eyes and that some were in the superficial layers of the superior colliculus. This is because this pathway is not anatomically bilateral (Edwards et al., 1979; Baleydier & Mauguiere, 1978) and the superficial layers of the superior colliculus do not receive input from the deep layers (Graham, 1977). To explain these experimental results one must appeal to less direct pathways which have been revealed using only visual stimulation, but may be used to suggest proprioceptive routes since there is no reason to believe these collicular neurons process information in a single modality.

One route by which the superior colliculus could receive binocular proprioceptive input is via the parabigeminal nucleus. The parabigeminal nucleus has been found to receive a strong retinotopically organized ipsilateral input from superficial (Graham, 1977; Graybiel, 1978; Baleydier & Mauguiere, 1978; Sherk, 1979) and deep layers of the superior colliculus (Baleydier & Magnin, 1979). Reciprocal connections from the parabigeminal nucleus to the superior colliculus are bilateral and, for the most part, maintain retinotopy (Baleydier & Magnin, 1979; Graybiel, 1978; Roldan, Reinso-Suarez, & Tortelly, 1983; Sherk, 1979). It is possible, therefore, that, through the parabigeminal nucleus, information received in the deep layers of the superior colliculus could be shared between the colliculi and perhaps with the superficial layers thus

accounting for the cells in the superficial layers which were responsive to extraocular muscle stimulation from both eyes.

Another pathway by which the superior colliculus could receive visual and proprioceptive information from the contralateral eye is through visual cortex. Updike (1977) has shown that visual cortex projects to the superior colliculus and Wickelgren and Sterling (1969) have shown that the visual binocularity of collicular cells is, to a great extent, contributed by visual cortex. Though no direct evidence is available that these corticofugal inputs to the superior colliculus provide proprioceptive signals, it is known that cells in visual cortex are sensitive to extraocular muscle proprioception (Ashton et al., 1984; Buisseret & Maffei, 1977) and it is thus plausible that cells in visual cortex could receive and relay this input to the superior colliculus.

In summary, the superior colliculus has been found to receive binocular visual and extraocular muscle proprioceptive input that could be important in mediating the monocular paralysis effect. Conversely, the parabigeminal nucleus, though it does project to the LGN (Hughes & Mullican, 1984), does not seem to receive substantial inputs other than those from the superior colliculus (Baleydier & Magnin, 1979) and has even been postulated to function as an extra-nuclear interneuron pool for the superior colliculus (Sherk, 1979). This does not mean that the parabigeminal nucleus is not important in the monocular paralysis effect, only that its activity relies entirely upon the functional integrity of the superior colliculus. Therefore, any lesion of the superior colliculus would similarly compromise the output of the parabigeminal nucleus to the LGN.

If the superior colliculus is in fact critical to the production of the monocular paralysis effect, then, with its lack of connectivity to the LGN, it must be shown how it exerts its control. The superior colliculus does project to other brainstem structures (the raphe nuclei and extensive parts of the

brainstem reticular formation: the tegmental reticular nucleus and the paralemniscal, lateral, magnocellular, and gigantocellular tegmental fields [Graham, 1977]) at least some of which have been shown to influence the excitability of geniculate cells (for reviews see Sherman & Koch, 1986; Singer, 1973; 1977). In addition, the superior colliculus may have a less direct role by projecting to other structures in the brain, such as the cerebellum or cortex.

Extraocular Muscle Proprioception in the Cerebellum

The cerebellum could receive extraocular muscle proprioceptive information from several places in the brain. The most direct route would be from the principal nucleus and the pars oralis. These nuclei send direct ipsilateral projections to the flocculus (Ito, 1984) and Larsell's lobules V-VIIIa (Gould, 1980; Ikeda, 1979). In addition to these inputs there are also projections to the cerebellum from the superior colliculus and cortex (which also contain neurons that are responsive to extraocular muscle stimulation [Ashton et al., 1984; Buisseret & Maffei, 1977; Donaldson & Long, 1980; Rose & Abrahams, 1975]) via the pons. The pontine nuclei receiving these projections are, however, thought to be purely visual (Baker, Gibson, Glickstein, & Stein, 1976; Mower, Gibson, & Glickstein, 1979) though response to eye muscle stretch per se has not been investigated in these structures. If the pontine nuclei did convey proprioceptive information to the cerebellum then the flocculus and paraflocculus could receive proprioceptive information via their connections with this structure.

The cerebellum could also receive extraocular muscle proprioceptive information via trigeminal inputs to the inferior olive. The spinal trigeminal nuclei (including the pars oralis), but not the principal nucleus, project to each of the three subdivisions of the inferior olive (Berkley & Hand, 1978; Walberg, 1982; Boesten & Voogd, 1975). The inferior olive has widespread input to the

cerebellum and could conceivably convey extraocular muscle proprioceptive information to lobules VI-VIII and flocculus (Gould, 1980).

Physiological recording of the cerebellum has revealed neuronal responses to eye muscle stretch and shock thus confirming the existence of these proprioceptive pathways. The proprioceptive responses from lobules Vb,c, VI, and VIIa,b have a latency as short as 4 msec and, interestingly, are anesthesia sensitive (Baker, Precht, & Llinas, 1972; Fuchs & Kornhuber, 1969; Schwartz & Tomlinson, 1977). Responses of contralateral and ipsilateral vermal cortex are equal suggesting a bilateral projection of proprioceptive fibers. In addition, units in lobule VI are found to respond to specific directions of eye movements (Schwartz & Tomlinson, 1977).

Floccular cells also respond to passive eye movements (Kimura & Maekawa, 1981). Consistent with this observation and the hypothesis that the flocculus has a major role in the production of the vestibulo-ocular reflex is the fact that a conduction block in the ophthalmic nerve by local anesthesia results in a reduction of the vestibulo-ocular reflex gain (Kimura, Takeda, & Maekawa, 1982; but see Magnin, Salinger, & Kennedy, 1986). The vestibulo-ocular reflex is also interesting because the gain and even the polarity of this reflex can be modified in adult subjects by wearing dove prism goggles, which reverse the right-left relations of the visual field (humans: Gonshor & Melvill-Jones, 1976a,b; cats: Robinson, 1976; Melvill-Jones & Davies, 1976). The time course of adaptation of the vestibulo-ocular reflex (Gonshor & Melvill-Jones, 1976b) is similar to that of the monocular paralysis effect (six days; unpublished observations). Together, these observations make the flocculus an attractive target of monocular paralysis experimentation.

Visual Pathways to the Cerebellum

The visuo-olivary pathways to the cerebellum involve two major sources, the superior colliculus and the pretectal nuclei. The superior colliculus projects

contralaterally to the caudomedial part of the medial accessory olive known as the subnucleus beta which then projects to lobule VII (Ito, 1984, pg. 268), the cerebellar uvula (Brodal, 1976; Courville & Farco-Cantin, 1978) and nodulus (Gould, 1980). These pathways are excited by large, contrast-rich moving stimuli presented to the contralateral eye (Ito, 1984, pg. 273; Simpson & Alley, 1974). Pretectal nuclei also send projections to the cerebellum via the olivary complex. These pathways provide visual information to lobules VI-VIII, the paramedian lobule (Ito, 1984, pp. 268-269; Gould, 1980; but see Hoddevick, Brodal, & Walberg, 1976), and flocculus (Ito, 1984).

Visual input to the pontine nuclei which also convey information to the cerebellum originates from two sources: 1) Visual Cortex (17, 18, 19, and lateral suprasylvian areas) to the ventromedial pons (Baker, et al., 1976) and 2) collicular input to the dorsolateral pons (Gould, 1980; Mower, et al., 1979). Visual neurons in both of these areas respond to no other modality and are powerfully driven by moving stimuli in the contralateral visual field from either eye. They are tuned for both direction and speed of movement, but the nature of the optimal stimulus is different between these two pathways: the corticopontine pathway is most responsive to large textured stimuli and the tectopontine pathway is most responsive to single spots (Baker et al., 1976; Mower et al., 1979). The paraflocculus and the uvula (and, to a minor extent, lobule VII) receive corticopontine input. The visual vermis (lobules VI-VIII) receive inputs from the tectopontine pathway.

The flocculus and lobules VI and VII may also receive visual input via the contralateral nucleus reticularis tegmenti pontis (NRTP; Ito, 1984, pg. 243). The NRTP may receive visual information from the ipsilateral pretectal area (mostly the nucleus of the optic tract) and the superior colliculus (Ito, 1984, pg. 244).

In summary, though proprioceptive and visual inputs to the cerebellum are too varied and complex to interpret fully at the present time, it is reasonable to hypothesize that because the cerebellum receives visual and proprioceptive input that it is involved in supporting the maintenance of the monocular paralysis effect. But how could the cerebellum exert an influence on the LGN?

Efferent Systems of the Cerebellum

Oculomotor dysfunctions that have been shown to arise after lesioning any of the cerebellar visual areas reveal that many cerebellar efferents project to oculomotor and pre-oculomotor nuclei in the brainstem. Of particular interest to the present study, however, is that none of the cerebellar nuclei project directly to the LGN (Ahlsen & Lo, 1982; Hughs & Mullikin, 1984; Leger, Sakai, Salvert, Touret, & Jouvet, 1975). This lack of a direct projection from the cerebellum to the LGN does not, however, rule out powerful though indirect cerebellar control over the LGN via other subcortical structures such as the brainstem reticular formation.

Brainstem Influences on Geniculate Processing

Early notions that the LGN functioned only as a visual relay nucleus (supported mainly by the fact that little elaboration of receptive field properties occurs at the geniculate level; Hoffmann, Stone, & Sherman, 1972; Hubel & Wiesel, 1961) are no longer tenable in light of research demonstrating the sensitivity of the LGN to extra-retinal input. Most telling is the observation that retinogeniculate projections account for only 10-20% of the synapses in the LGN. The rest of these synapses are contributed mostly by visual cortex, with perigeniculate cells, geniculate interneurons, midbrain reticular formation, brainstem reticular formation (including the locus coeruleus, the parabrachial nucleus, and the dorsal raphe nucleus), and pontine reticular formation supplying most of the remaining input (Sherman & Koch, 1986). It seems reasonable to assume that these extraretinal inputs, as massive as they are,

have some effect on relay of visual signals to cortex. Many effects mediated by these extra-retinal inputs have already been described (for reviews see Sherman & Koch, 1986; Singer, 1973; 1977).

The cerebellum has projections to the brainstem areas whose activity has been shown to modulate transmission of visual information through the LGN. The fastigial nucleus, one of the three cerebellar nuclei that provide output from the cerebellum, projects directly to the raphe nucleus (Asanuma, Thach, & Jones, 1983), the locus coeruleus (Snider, 1975), and portions of the pontomesencephalic reticular formation (Walberg, Pompeiano, Westrum, Hauglie-Hansen, 1962) which are all parts of the brainstem reticular formation. The vestibular nuclear complex is another, separate, output from the cerebellum which may provide input to the reticular formation. It is through these nuclei, then, that the cerebellum may serve to modulate LGN activity, perhaps in service of the binocular-visual/proprioceptive integrative processes shown to be involved in the monocular paralysis effect. This possible cerebellar modulation of LGN activity may, then, be revealed by reversal of the monocular paralysis effect as a consequence of cerebellar lesion.

Summary and Hypotheses

It has been shown that the change in relative encounter rates of X and Y cells that occur as a result of monocular paralysis exhibits characteristics which mimic (and, therefore, model) certain aspects of strabismic amblyopia. This similarity may not be accidental, but may be indicative of the fact that both of these phenomena reflect the operation of binocular-visual/proprioceptive integrative mechanisms which modulate the transmission of visual information through the LGN. Therefore a study of monocular paralysis may yield information, not only about strabismic amblyopia, but also about these binocular-visual/proprioceptive integrative mechanisms. Further, since the changes that occur as a result of monocular paralysis are manifested in the

adult, this preparation represents an example of adult plasticity, the demonstration of which raises questions about its purpose in the normal cat and the locus of the changes that occur.

Questions about the nature of the monocular paralysis effect which may yield clues about the etiology of strabismic amblyopia and the nature of binocular-visual/proprioceptive integrative mechanisms and their plasticity may be answered, in part, by an analysis of the neural circuitry which supports the monocular paralysis effect. Both the cerebellum and superior colliculus have been shown to receive substantial proprioceptive and visual information and have direct or indirect connections to the LGN that could allow them to be involved in the integration of binocular proprioceptive information with binocular visual information which has been implicated in the monocular paralysis effect.

Therefore, it was the purpose of this study to test the hypothesis that the superior colliculus and/or the cerebellum are involved in the maintenance of the monocular paralysis effect by first confirming the X cell encounter rate shift subsequent to monocular paralysis and then, after lesioning the superior colliculus or cerebellum, again recording to determine if the X cell encounter rate had been restored by the manipulation. Logically, there are four alternative hypotheses possible: 1) lesion of the cerebellum reverses the monocular paralysis effect as does lesion of the superior colliculus; 2) cerebellar lesion reverses the monocular paralysis effect, but collicular lesion does not; 3) cerebellar lesion does not reverse the monocular paralysis effect, but collicular lesion does; and 4) neither cerebellar nor collicular lesion reverses the monocular paralysis effect. A 2 (lesion type: collicular and cerebellar) x 3 (recording condition: pre-lesion sedated, pre-lesion anesthetized, and post-lesion) x 2 (lamina: A and A1) design was used to test these hypotheses.

CHAPTER II

METHOD

Experimental Conditions and General Procedure

Eight adult cats were monocularly paralyzed by surgical transection of cranial nerves III, IV, and VI. After a period of this surgically induced paralysis, the encounter rate of X cells (always relative to the encounter rates of Y cells and unclassified cells) was determined in two phases: pre-lesion and post-lesion. The first phase of recording was completed to assess the magnitude of the monocular paralysis effect and, hence, provide a criterion by which to evaluate the increase in the X cell encounter rate after cerebellar or collicular lesion. The magnitude of the monocular paralysis effect (the typically low X cell encounter rates found in monocularly paralyzed cats) was estimated via the paired-pass technique in which the X cell encounter rate is assessed in each of two penetrations made through the same location in the LGN, one when the cat is sedated and the other when the cat is anesthetized (Schroeder et al., 1988; Schroeder, Salinger, Hoffmann, & Guido, 1984). Since anesthesia abolishes the monocular paralysis effect (increases the X cell encounter rate) the difference in the X cell encounter rates between these paired penetrations corresponds to the magnitude of the monocular paralysis effect. This initial phase completed, animals received either a cerebellar or collicular lesion after which the second phase of recording commenced. The post-lesion phase of recording consisted only of one penetration through the LGN during which the X cell encounter rate was determined in the sedated condition at the approximate location of the pre-lesion paired-pass. This final determination of the X cell encounter rate was

made to test the hypothesis that the lesion had abolished the monocular paralysis effect as the pre-lesion anesthetized condition had.

Anesthesia

A discussion of anesthesia and its manipulation is necessary not only because surgery and other potentially painful procedures demand its use, but because it is used as a condition of the paired-pass recording technique discussed above. Since, depending on the dose, the effects of sodium pentobarbital can range from mild sedation to deep anesthesia, this barbiturate was selected to manipulate the anesthesia level for the paired-pass as well as to prepare the animal for surgery. Sedation is defined as the presence of corneal blink and tendon reflexes, normal respiration, and acceptance of painless head restraint together with the capability of ataxic locomotion and feeding. To achieve the sedated state the cat was given initial intraperitoneal injections of 2.9 mg/kg acepromazine maleate and 5 mg/kg sodium pentobarbital with intravenous supplements of sodium pentobarbital as needed. The anesthetized state, behaviorally defined as the absence of corneal blink and tendon reflexes as well as abdominal instigation of the inspiratory phase of respiration (stage III, plane 2 anesthesia; Cohen, 1975), was attained by additional doses of sodium pentobarbital (given either intraperitoneally or intravenously) to the already sedated animal. Once the pre-determined anesthesia state was reached it was carefully maintained by additional injections of sodium pentobarbital as needed.

Apart from the definition of anesthesia/sedation states for the purpose of experimental manipulation, is the question of the adequacy the prevention of pain on purely ethical grounds during all phases of the experiment. For the sedated state, we can be reasonably confident that the subjects were pain-free because, insofar as the cats could react to mildly noxious stimuli (such as toe pad pinch) or move if merely restless, the animals demonstrated their ability to

respond overtly if in pain during the recording session. Any movement would be intolerable during physiological recording thus assuring that barbiturate was administered in quantities sufficient to prevent discomfort. In the anesthetized state (stage III, plane 2) the animal does not respond to noxious stimuli (such as toe pad pinch, corneal stimulus, or even surgical manipulations) thus demonstrating its insensitivity to otherwise painful stimuli.

Subjects and Surgical Preparation

Subjects were eight domestic cats (Felis domesticus), acquired at the Guilford County Animal Shelter (North Carolina), weighing at between 2.7 and 5.3 kg, and were housed and maintained according to USDA regulations.

Experimentation on each subject began with monocular paralysis as first described by Brown and Salinger (1975). After induction of anesthesia, a ventral approach through the soft palate and the sphenoid sinus was made until the optic nerve, optic chiasm, and optic tract, all still incased in bone, could be visualized. Cranial nerves III, IV, and VI, lying just dorsal of the cavernous sinus, were at this point also encased in bone just ventral and lateral to the optic chiasm. Taking care to respect the bony protection of the visual afferents, drilling proceeded laterally to expose the cranial nerves at a common point of entry into the orbit and here they were transected. The bony covering and dura protecting the optic chiasm and cranium remained intact therefore ruling out the possibility of damage occurring to the optic nerve or central visual structures. Bonewax, gelfoam, and epinephrine hydrochloride were used to control bleeding during surgery and temperature and respiration were maintained at normal levels. The wound was flooded with penicillin before closure and the animal was started on a regimen of systemic antibiotics to provide protection from post-operative infection.

On the fifth post-operative day, the animal was again anesthetized and placed in a stereotaxic apparatus. The skull was then exposed and its

periosteum (tissue carrying pain sensitive nerve fibers) removed. After the method of Orem, Schlag-Rey & Schlag (1973), a pedestal was fashioned from dental acrylic and attached to the head with screws cemented into the skull. Bolts protruding from the top of this pedestal could then be fastened to the stereotaxic apparatus via a specially made adapter thus permitting rigid support of the head in the stereotaxic plane without recourse to painful eye and ear bars.

Two craniotomies were also performed, one over the optic chiasm (OX) and the other over the caudal extreme of the optic tract (OT) and LGN to allow for macroelectrode implantation in the OX and OT and microelectrode recording in the LGN. Using electrophysiological criteria, bipolar electrodes (twisted, teflon coated stainless steel wire, tip separation 2.5 mm OX and 2.0 mm OT) were positioned within the optic chiasm (Horsley-Clarke coordinates A 13.5 and L 0.0) and the caudal extent of the optic tract (A 8.0 and L 10.5). These macroelectrodes were then permanently implanted with dental acrylic for later use as stimulating electrodes.

Preparation for recording. Beginning on the sixth post-operative day the animal was sedated and placed in the stereotaxic apparatus using the painless head restraint device. The paralyzed eye was protected from desiccation by a zero power contact lens. The tear film of the non-paralyzed eye was adequate to avoid the need for a contact lens. The optic disk of the paralyzed eye was then mapped on a tangent screen 1 m away (Fernald & Chase, 1971) thus providing a landmark from which to calculate the position of the vertical and horizontal meridians (corresponding to the center of the area centralis) with an accuracy of +/- 2° (Vakkur, Bishop, & Kozak, 1963). Receptive field locations of cells in lamina A are given as angular distance from the center of gaze and only those cells whose receptive fields are located within the central 10° of visual space were included in the data analysis. Locations of A1 fields were

assumed to correspond to the location of cells recorded in A since the receptive field maps of these two laminae are known to be in register (Sanderson, 1971). The paralyzed eye was then refracted, if necessary, by spectacle lenses and the clear contact lens replaced by one with an artificial pupil of 3 mm in diameter to improve optics.

Recording. Neuronal activity was sampled with a tungsten microelectrode (Haer Instruments, rated 30 MΩ at 1000 Hz), amplified with a WPI DAM-5 preamplifier, monitored auditorially, and displayed on a Tektronix T912 storage oscilloscope. The electrode was advanced through the LGN with a hydraulic microdrive (David Kopf Instruments) controlled by a stepper and interface (Oriel) while the eyes were visually stimulated (Grass PS22 photo stimulator). If no isolated units were encountered within 100 μm of the last cell encountered additional measures to drive units were taken such as application of chiasm shock or waving visual stimuli (wands) in the line of sight.

Once adequate isolation of a cell body (as distinguished from axons by the criteria of Bishop, Burke, & Davis, 1962) was achieved the cell was classified as an X or Y cell on the basis of a battery of five receptive field tests and conduction velocity (CV). Receptive field tests were performed on units with action potentials large enough to isolate with a window discriminator (W-P Instruments, Model 120). Visual stimuli were produced by a Picasso image synthesizer (Innisfree) and controlled by an IBM PC-XT computer in conjunction with an interfacing computer (Cambridge Electronic Design, Model 1401). These images were presented on a monitor (Tektronix model 608) placed 1 m from the cat's eyes, at which distance the oscilloscope face subtended 5.6°. Sinusiodal gratings and flashing spots of 86% visual contrast [defined as 100 x $(L_{max} - L_{min})/(L_{max} + L_{min})$] were used for the receptive field tests. The mean luminance [defined as $(L_{max} + L_{min})/2$] of the scope face was 12.6 cd/m^2 for grating patterns; mean luminance for spots depended on the size of the spot.

The receptive field tests included: 1) Size of the excitatory center of the receptive field as determined with a flashing spot of light (X < 1° , Y > 1°; Cleland, Dubin, & Levick, 1971); 2) Spatial frequency resolution using a 2 Hz drifting grating (X: modulated response at 1 cycle/degree or greater, Y: modulated response only at lower spatial frequencies; So & Shapley, 1979); 3) the response of a unit to the sudden reversal of the entire receptive field to the center-excitatory stimulus (X: no response, Y: response burst; Cleland et al., 1971); 4) center-surround receptive field antagonism (X: response attenuation as the size of a flashing spot is increased to include the inhibitory surround, Y: little or no attenuation; Bullier & Norton, 1979); 5) Index of linearity of spatial summation across the receptive field of the cell (Enroth-Cugell & Robson, 1966; Hochstein & Shapley, 1976; So & Shapley, 1981). For the linearity index, counterphase and drifting gratings of eight different spatial frequencies (interleaved, including a "noise" screen- luminance matched, lacking contrast) were presented as the cell's responses were stored as post-stimulus time histograms (PSTHs). Powers of the 1st and 2nd harmonics (elicited by the drifting and counterphasing gratings, respectively, 3 cycles/sec) were determined by fast Fourier transform (FFT) performed on each of these 2048 msec epochs and averaged across 10 trials. T-tests were used to compare the powers of these harmonics elicited at the various spatial frequencies to those elicited by the "noise" screen. For those spatial frequencies at which the 2nd harmonic response was significantly higher than noise, the highest ratio of 2nd harmonic to 1st harmonic was taken as the linearity index. A linearity index of 1 or more was considered to be Y-like; lower values were considered to be X-like.

CV was determined by dividing the distance between the OX and OT electrodes by the difference in response latency to shock from each electrode (delivered by a Grass S8 stimulator and SIU5 stimulus isolation unit). LGN

cells whose retinal afferents displayed a CV less than 25 m/s were classified as X cells and those with faster CVs were classified as Y cells (Cleland et al., 1971; Garraghty et al., 1982; So & Shapley, 1979). Stimulation of retinal afferents by the OT electrode resulted in a latency measurement greater than .7 msec (clearly a latency greater than that noted for direct stimulation of neurons) and always with some amount of "jitter" thus indicating that the LGN neurons were not being stimulated directly by the OT electrode which lay close to the LGN.

Disagreement of any more than one of the receptive field and CV tests resulted in the labeling of the cell as non-classifiable.

The paired-pass. In preparation for paired-pass recording, the animal was randomly assigned to be either anesthetized or sedated. While this assigned state was maintained, the X cell encounter rate was assessed in an area of the LGN representing the central 10° of visual space. Cooling of visual cortex ipsilateral to the LGN being recorded from was occasionally substituted for the anesthesia member of the paired-pass since this manipulation has been shown to have the same effect on the X cell encounter rate as anesthesia (Moore, Vaughan, Salinger, Willis, & Cole, 1988). Once this initial penetration through the LGN was completed, the electrode was retracted to the dorsal-most extreme of the LGN and the anesthesia state (or cortical temperature condition) of the animal was reversed to the alternate condition (e.g., if the LGN was first recorded while the cat was sedated, the second recording pass was completed while the cat was anesthetized (or ipsilateral visual cortex cooled). The electrode, held in position by the stability of the surrounding tissue, could then be passed through very nearly the same area as before and the X cell encounter rate reassessed. The purpose of this second pass was not to record from the same cells, but to sample from the same area of the LGN to reduce the amount of variance in the X cell encounter rate data related to receptive field

eccentricity (Hoffmann et al., 1972). If there had been an effect of monocular paralysis, then there would be a higher proportion of X cells in the anesthetized (or cortical cool) condition relative to the sedated condition. The direction of the difference between the two passes is taken to show the presence of the monocular paralysis effect in the sedated condition (Garraghty et al., 1982; Schroeder et al., 1988). The size of the difference establishes a standard by which the effect of further surgical manipulations can be assessed.

Cerebellar lesions. Once the subject was anesthetized the scalp was reflected to the base of the skull and a craniotomy made in the interparietal and occipital bones protecting the cerebellum. Taking care to avoid damage to brainstem structures, the cerebellar cortex and underlying peduncles were aspirated. The wound was then sealed with gelfoam and the cat allowed to recover from anesthesia to permit recording under the sedated condition.

Lesions of visual cortex (areas 17, 18, and 19 contralateral to recorded LGN) in cats used in another experiment functioned as surgical controls for the cerebellar lesions (Moore et al., 1988). In this control experiment monocularly paralyzed cats were prepared for chronic recording as in the present study. The X cell encounter rate was then assessed and the reduced values typical of monocularly paralyzed cats were observed. Then, under surgical anesthesia a craniotomy of the occipital bone was made over the right hemisphere. Areas 17, 18, and 19 of cortex ipsilateral to the LGN being recorded were then aspirated and the wound closed. Subsequent assessment of the X cell encounter rate in the LGN revealed that values were comparable to X/Y ratios measured under anesthetized conditions and were significantly higher than pre-lesion sedated LGN penetrations (5 cats, 92 cells, $p < .001$). This was in direct contrast to X cell encounter rates which were measured after the visual cortex contralateral to the LGN being recorded was aspirated. These post-lesion X cell encounter rates no higher than during the pre-lesion sedated LGN penetrations

(4 cats, 96 cells, $p > .05$). Therefore, the removal of visual cortex contralateral to the recorded LGN is a logical control for the cerebellar lesions because it results in similar surgical trauma and possible residual effects of anesthesia, but does not influence the X cell encounter rate in monocularly paralyzed cats.

The fact that the post-lesion condition cannot be completed first, followed then by the pre-lesion conditions, implies the possibility that order effects could contribute to a presumed effect of a lesion on the relative encounter rates for X and Y cells. The fact that the cerebellar and collicular lesions are not reversible does not, however, detract from the present experimental design because order effects have never been observed in experiments measuring the encounter rates for X and Y cells in monocularly paralyzed cats in which the further manipulations aimed at assessing the suppression of X cells were reversible (anesthesia [Guido et al., 1988; Schroeder et al., 1988] and cortical cooling [Moore et al., 1988]).

Collicular lesions. Under anesthesia, the right parietal bone was exposed and a craniotomy of its medial aspect performed. A recording/lesioning electrode (teflon-coated stainless steel wire, 0.010 in. diameter, insulated except for the tip) was then positioned in the region of the superior colliculus (approximate Horsley-Clarke coordinates A 2.0 and L 3.0) whose visual receptive fields, recorded during electrode placement, were in central visual space and overlapped those of geniculate cells recorded during the pre-lesion recording penetrations. Electrical current (averaging 1.6 mAmps) was then passed monopolarly through this electrode to produce the lesion. At pre-determined intervals lesioning was ceased and, after a period of stabilization, the responsivity of the adjacent collicular tissue to visual stimulation (as measured at the lesioning electrode) was reassessed. This assessment was made by waving hand held wands through central visual space and noting the

response both auditorially (over the audiomonitor) and visually (with the oscilloscope). Lesioning was continued until visual stimulation in central visual space no longer produced a collicular response detectable above background.

Histology

Once recording was completed the animal was given a lethal overdose of sodium pentobarbital and perfused with neutral buffered 10% formal saline. The brain was then extracted and the distance between the OX and OT electrodes determined to permit calculation of CVs as described above. For collicular lesions, the brainstem was then frozen and serially sectioned. A subset of the sections were mounted and examined for extent and placement of the lesion and accidental damage to brainstem structures. For cerebellar lesions the brain was examined grossly to determine the completeness of the lesion and a photographic record made of its extent.

Statistical Methods

The relative encounter rates of X, and Y, and unclassified cells recorded under pre-lesion sedated and anesthetized conditions and under the post-lesion condition (either collicular or cerebellar) were determined. The predicted increase of the X cell encounter rates obtained during the pre-lesion anesthetized and post-lesion conditions of recording relative to the X cell encounter rates obtained during the pre-lesion sedated condition was then assessed by analysis of variance using X cell encounter rates obtained in each of these three conditions in each cat as the unit of measure. The analysis of variance consisted of one between groups factor: lesion type (collicular or cerebellar), and two within subjects factors: recording condition (pre-lesion sedated, pre-lesion anesthetized, and post-lesion) and lamina (A and A1). Post-hoc comparisons were accomplished via orthogonal contrasts (Keppel, 1982).

CHAPTER III

RESULTS

For eight animals, the relative encounter rates of X, Y, and unclassified cells were measured under three conditions after an initial period (six days) of monocular paralysis: 1) Pre-lesion sedated, 2) Pre-lesion anesthetized, and 3) Post-lesion (either cerebellar lesion or electrolytic lesion in the superior colliculus, recorded under sedation levels of anesthesia). These encounter rates, presented as individual data in Appendix A, are based on extracellular recordings made from a total of 414 cells in the right LGN in portions of laminae A and A1 representing the central 10° of visual space. Collection of data for each of the three conditions was accomplished by successive penetrations in approximately the same location to insure, as described in Methods, that changes in the relative encounter rates of X and Y cell were due only to the change of recording condition, not location.

Cerebellar Lesions

Figures 1 and 2 present data from four cats that were recorded under two pre-lesion levels of anesthesia (sedated and anesthetized) and post-cerebellar lesion and displays the mean encounter rates of each cell type by condition for the A and A1 laminae, respectively. It can be seen that in both laminae there was a highly reliable increase in encounter rates for X cells in the anesthetized relative to the sedated condition (A lamina: $p < .0014$, orthogonal contrasts, $df = 1,16$; A1 lamina: $p < .0001$). (The F-table for this and all other ANOVAs may be found in Appendix B.) The encounter rate of unclassified cells was small (3.4% overall) and did not change significantly between conditions. Thus, the change in encounter rates for X and Y cells was always nearly

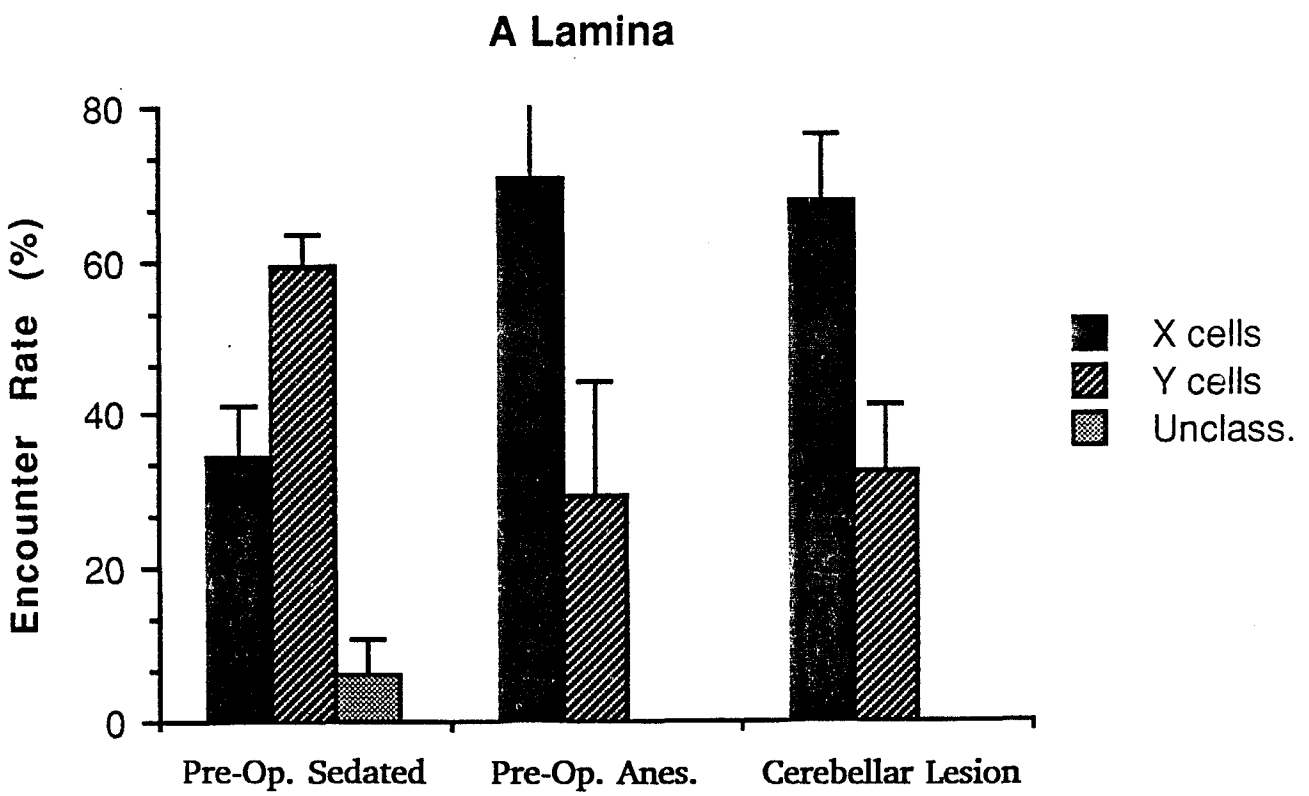

Figure 1. The relative encounter rates of X, Y, and unclassified cells in the A lamina for three conditions: Pre-lesion sedated, pre-lesion anesthetized, and post-cerebellar lesion. The means for a total of 4 cats are shown, bars represent standard error of the mean.

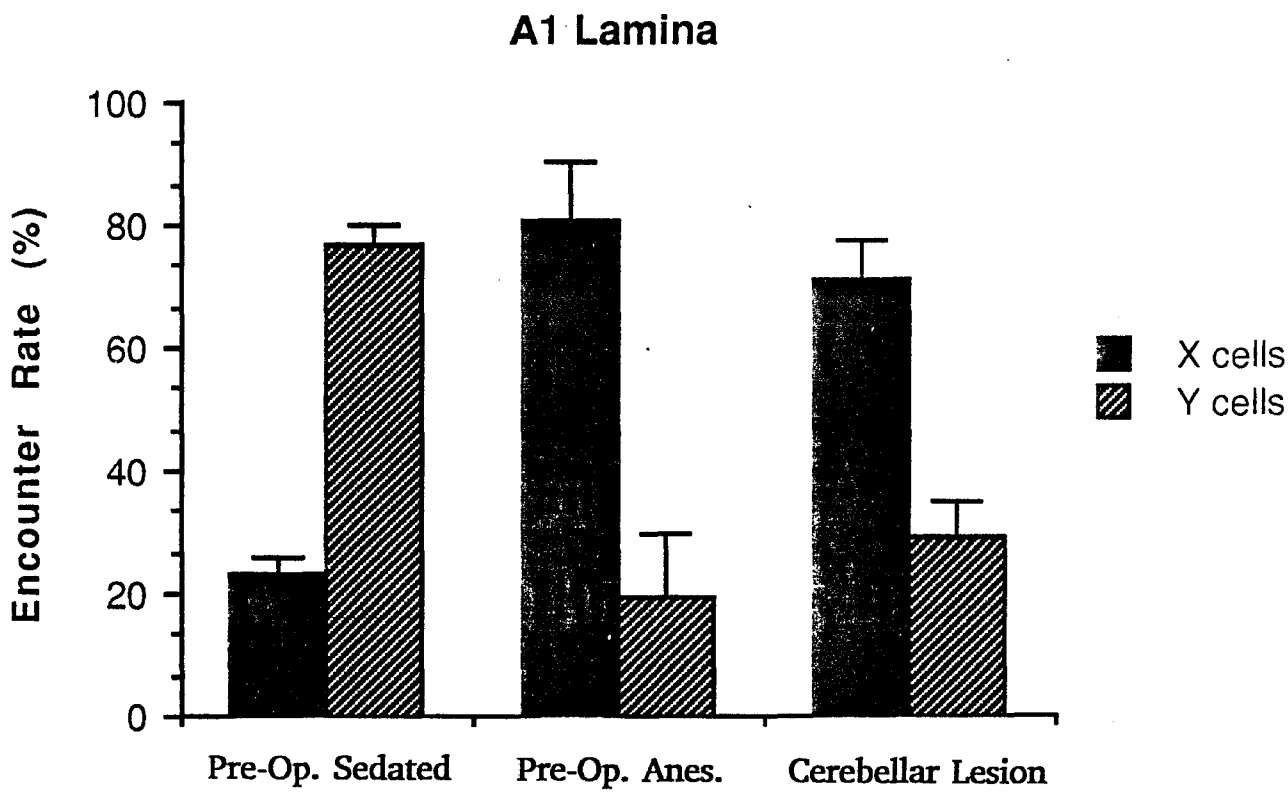

Figure 2. The relative encounter rates of X, Y, and unclassified cells in the A1 lamina for three conditions: Pre-lesion sedated, Pre-lesion anesthetized, and Post-cerebellar lesion. The means for a total of 4 cats are shown, bars represent standard error of the mean.

reciprocal, permitting us to report all effects in terms of X cell encounter rates only.

The cerebellar lesion condition also shows a very reliable increase in the encounter rate of X cells relative to the sedated condition in both laminae (A lamina: $p < .02$, orthogonal contrasts, $df = 1,17$; A1 lamina: $p < .0004$) that cannot be distinguished from that of the Pre-op. anesthetized condition (A and A1 laminae: $p > .05$ for t-test, $df = 17$). Thus, the cerebellar lesion induced an increase in the encounter rate of X cells relative to the sedated condition indistinguishable from that of the anesthetized condition.

Since there is reason to hypothesize that brainstem damage could alter the relative excitability of X and Y cells just as anesthesia does (see Introduction), it was necessary to determine if any such damage had occurred during the aspiration procedure. Upon examination, the lesions were found to be confined to the cerebellum in each case. A representative lesioned brain is shown in Figure 3 along with, for comparison, a normal intact brain shown also with the cerebellum completely dissected away to expose the brainstem. Clearly, a much more radical lesion would have been necessary to damage brainstem which lies ventral to the cerebellum. This is also the case for the three remaining lesions, shown in Appendix C.

A visual comparison of the lesions yielded no obvious differences between the locations or extents of cerebellar damage. In all cases, the dorsal vermis and underlying white matter were aspirated sparing the lateral and posterior vermis, and, of course, those most ventral cerebellar lobules lying juxtaposed to the pons. Any undetected variability that was present in the cerebellar lesions was apparently not sufficient to cause a similar variation in the post-lesion encounter rates for X cells- the increase relative to the sedated condition was noted in every subject.

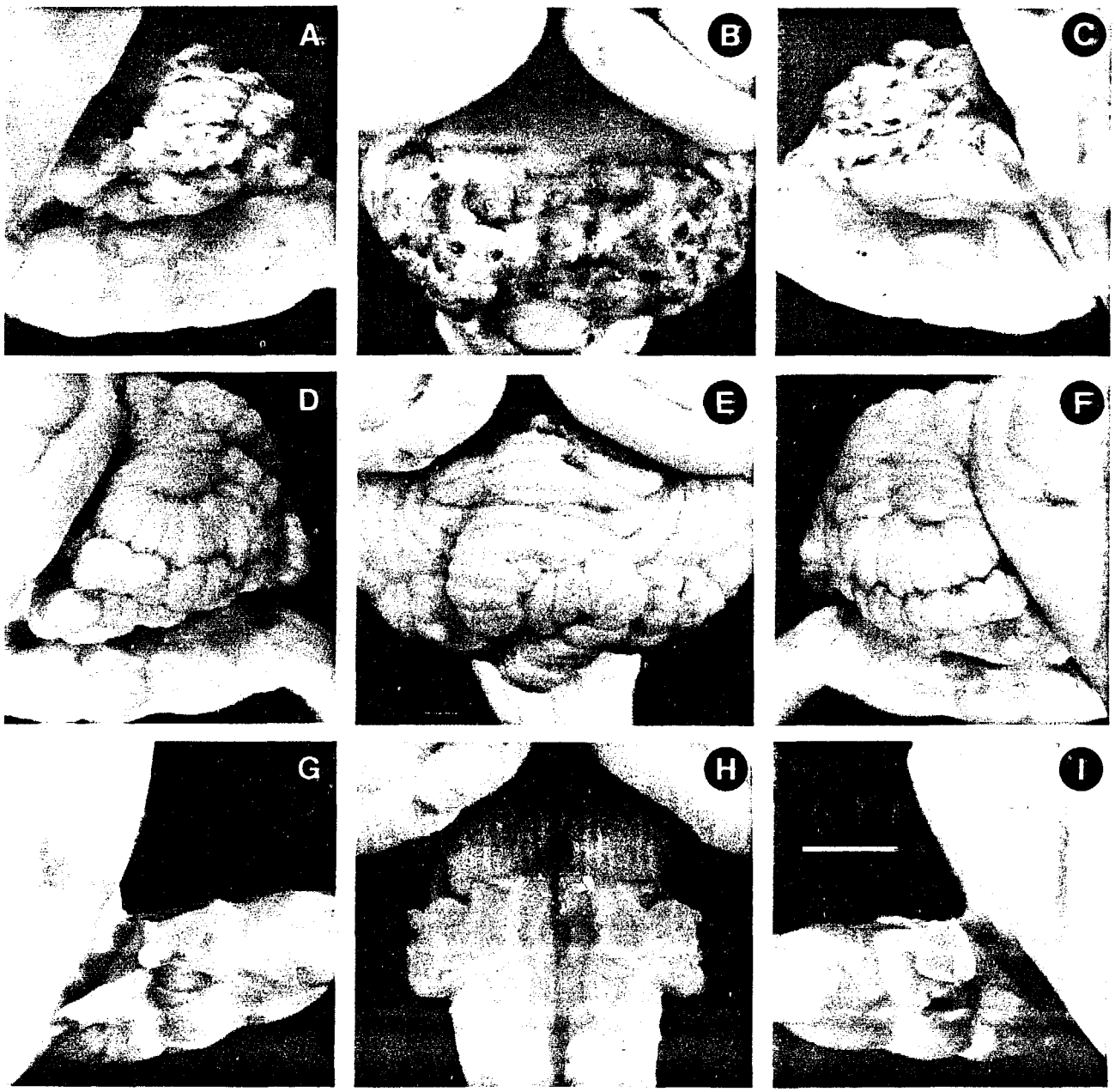

Figure 3. Left side, right side, and dorsal views of cerebellar lesion #1198 (A-C, respectively) presented with, for comparison, a normal brain (D-F) shown also with the cerebellum completely dissected away to expose the pons (G-I). Note that a much more radical lesion of the cerebellum would have been necessary to destroy underlying brainstem. Scale bar represents 5 mm.

Collicular Lesions

Figures 4 and 5 present data from four cats that were recorded under two pre-lesion levels of anesthesia (sedated and anesthetized) and post-collicular lesion and displays the encounter rates of X, Y, and unclassified cells by condition for the A and A1 laminae, respectively. It can be seen that there was an increased encounter rate for X cells in the anesthetized condition relative to the sedated condition in both laminae (A lamina: $p < .008$, orthogonal contrast, df = 1,17; A1 lamina: $p < .0002$). Furthermore, t-tests indicate that the sedated and anesthetized conditions for the A and A1 data for the collicular lesion subjects are very similar to those for the cerebellar lesion subjects (A laminae, sedated: $p > .8$, df = 6; A1 laminae, sedated: $p < .10$, df = 6; A laminae, anesthetized: $p > .8$, df = 5; A1 laminae, anesthetized: $p < .5$, df = 5). However, orthogonal contrasts show that the X cell encounter rate for the collicular lesion condition was not significantly higher than that of the sedated condition in either laminae (A lamina: $p < .18$, df = 1,17; A1 lamina $p < .99$, df = 1,17) or, by t-test, in both lamina combined ($p > .05$, df = 17). Therefore, the collicular lesion did not have the effect of increasing X cell encounter rates as did the cerebellar lesions. Further, this finding cannot be attributed to a higher than normal X cell encounter rate prior to the collicular lesions since, as shown above, animals from the two groups did not differ in this regard.

Failure to detect an increase in the X cell encounter rate in the collicular lesion condition makes it especially important to demonstrate the accuracy and extent of the electrolytic lesions. A reconstruction of each collicular lesion, an example of which appears in Figure 6, was created by taking coronal slices (20 μm thickness) that represented the geometric center of each lesion as well as its rostral and caudal extreme and exposing a photographic emulsion to the enlarged image of the unstained slide. Inspection of these reconstructions, the

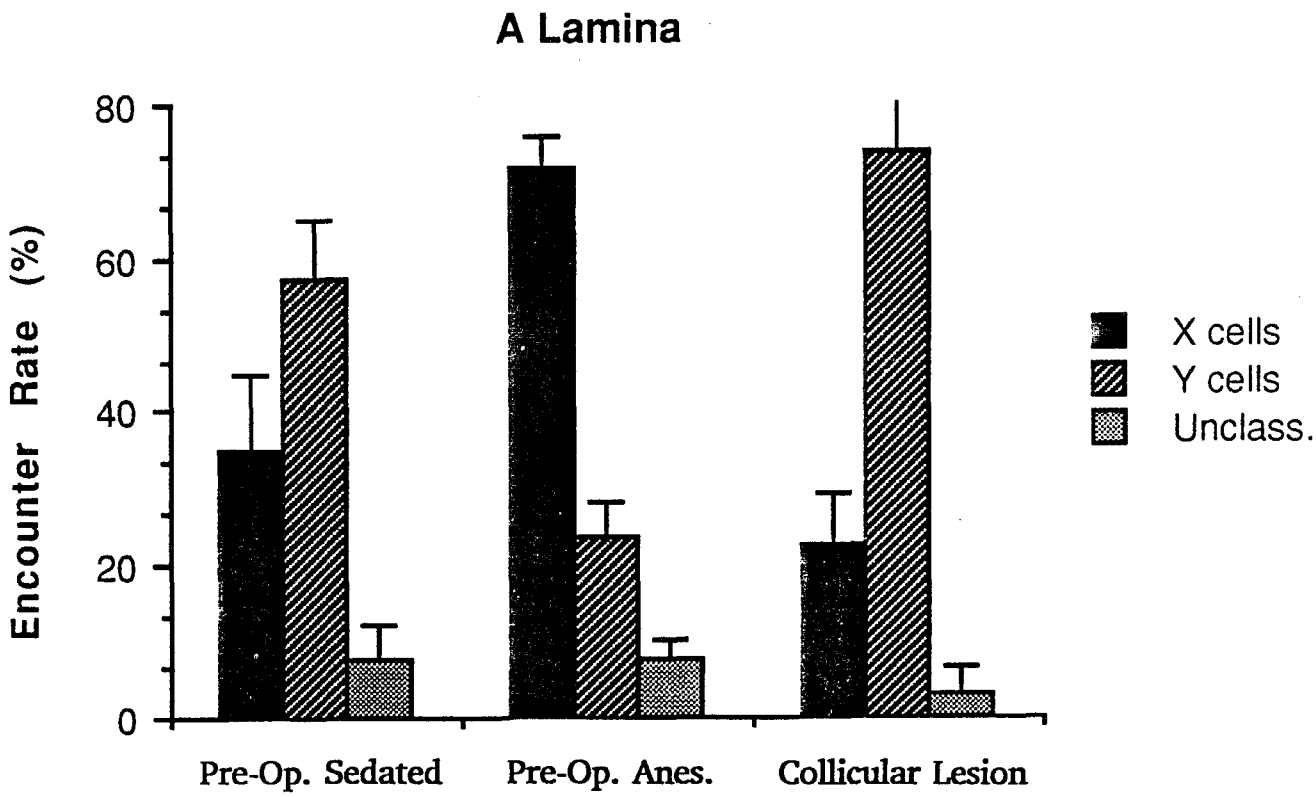

Figure 4. The relative encounter rates of X, Y, and unclassified cells in the A lamina for three conditions: Pre-lesion sedated, Pre-lesion anesthetized, and Post-collicular lesion. The means for a total of 4 cats are shown, bars represent standard error of the mean.

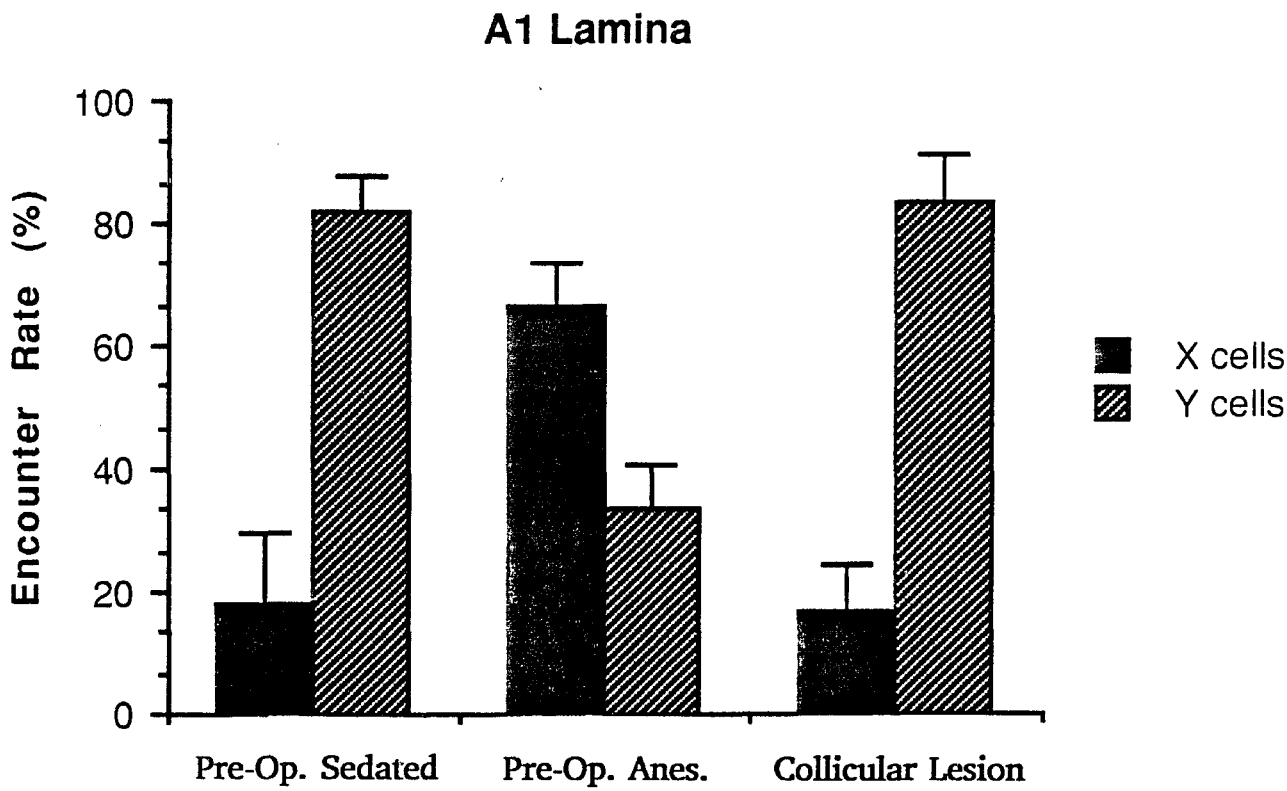

Figure 5. The relative encounter rates of X, Y, and unclassified cells in the A1 lamina for three conditions: Pre-lesion sedated, Pre-lesion anesthetized, and Post-collicular lesion. The means for a total of 4 cats are shown, bars represent standard error of the mean.

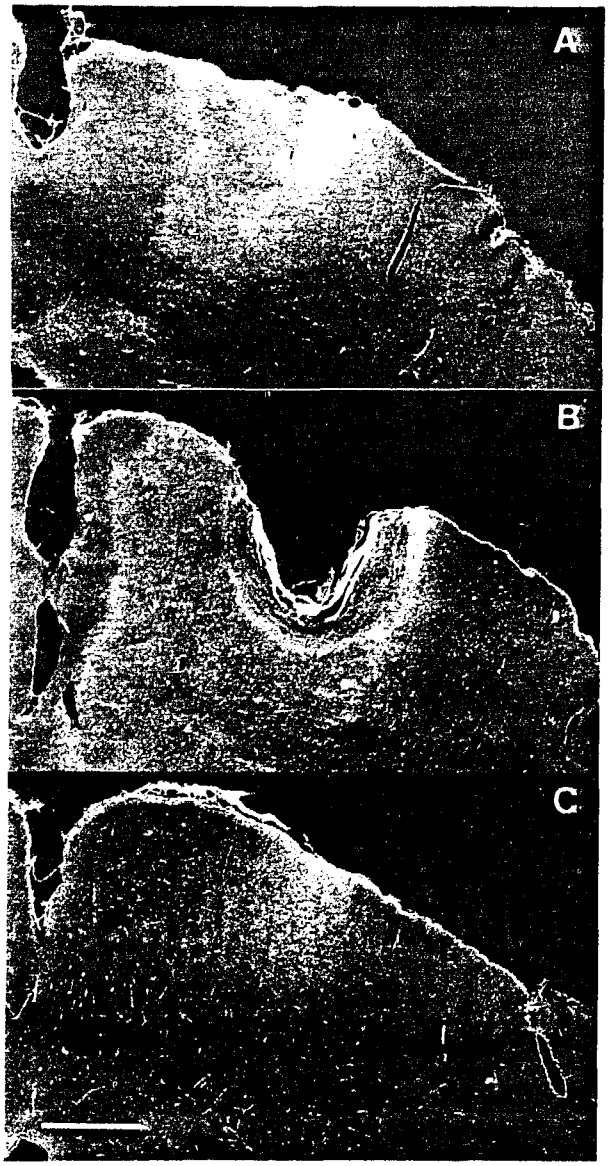

Figure 6. Three views of collicular lesion #1316 are shown. A photographic emulsion was exposed to the enlarged image of unstained slides (20 μm thick, 1.1 mm apart) representing the rostral extreme (A), the geometric center (B), and caudal extreme (C) of the electrolytic lesion. The lesion was created by 1.26 Amp-seconds of current passed through a monopolar electrode (teflon-coated medwire, 0.010 in. diameter, insulated except for the tip,). Scale bar represents 1 mm.

remaining examples of which appear in Appendix D, reveals that in each case the lesion was confined to the superior colliculus (compare Figure 7) and thus the null result could not be due to any incidental damage to structures ventral to the colliculus.

The validity of the present finding also rests on the placements of these lesions relative to the collicular representation of central visual space. As detailed in the Method, these lesions were placed physiologically in collicular representations of the LGN penetrations and current was applied until that area of the superior colliculus was no longer recordable. Corroboration of these placements can be obtained using a retinotopic map (Berman & Cynader, 1972; Feldon, Feldon, & Kruger, 1970) of the superior colliculus and comparing it to a graphical representation of the lesion. (See Figure 8 for an example; the remaining lesions are presented in Appendix E.) The variability that is present may, in fact, be real but the physiological evidence suggests the alternative explanation that there is variability between subjects in the retinotopic representations of central visual space. In any case, the anatomical evidence suggests that even though there is variation in the placements of the lesions, there is considerable overlap within the targeted area. This strengthens the conclusion that collicular lesions do not increase the X cell encounter rate as anesthesia and cerebellar lesion do because no subject exhibited an increase in the X cell encounter rate when the data were collapsed across laminae.

In conclusion, the location and size of the electrolytic collicular lesions were adequate to destroy areas that were retinotopically matched to the recording penetrations within the LGN. These lesions, however, did not destroy more ventral brainstem locations and therefore the finding that there was no post-lesion increase in the X cell encounter rate cannot be accounted for by accidental damage or any variation in the location of the lesion site. In the aggregate they suggest that a much larger collicular lesion would have also had

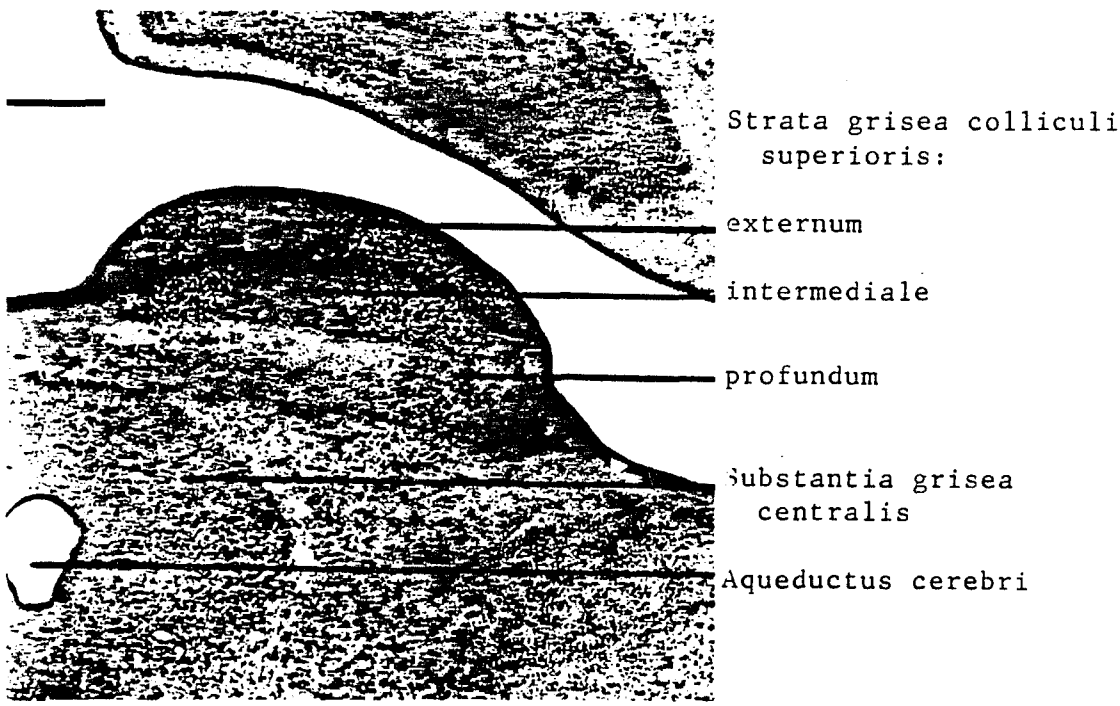

Figure 7. A nissl stained coronal slice at AP 2.0 mm from a normal superior colliculus. Strata of the right colliculus (externum, intermediale, and profundum) are labeled to facilitate comparison of the lesion depth relative to the colliculus in Figure 6. Scale bar (upper left) represents 1 mm. Reproduced from Snider and Niemer (1961).

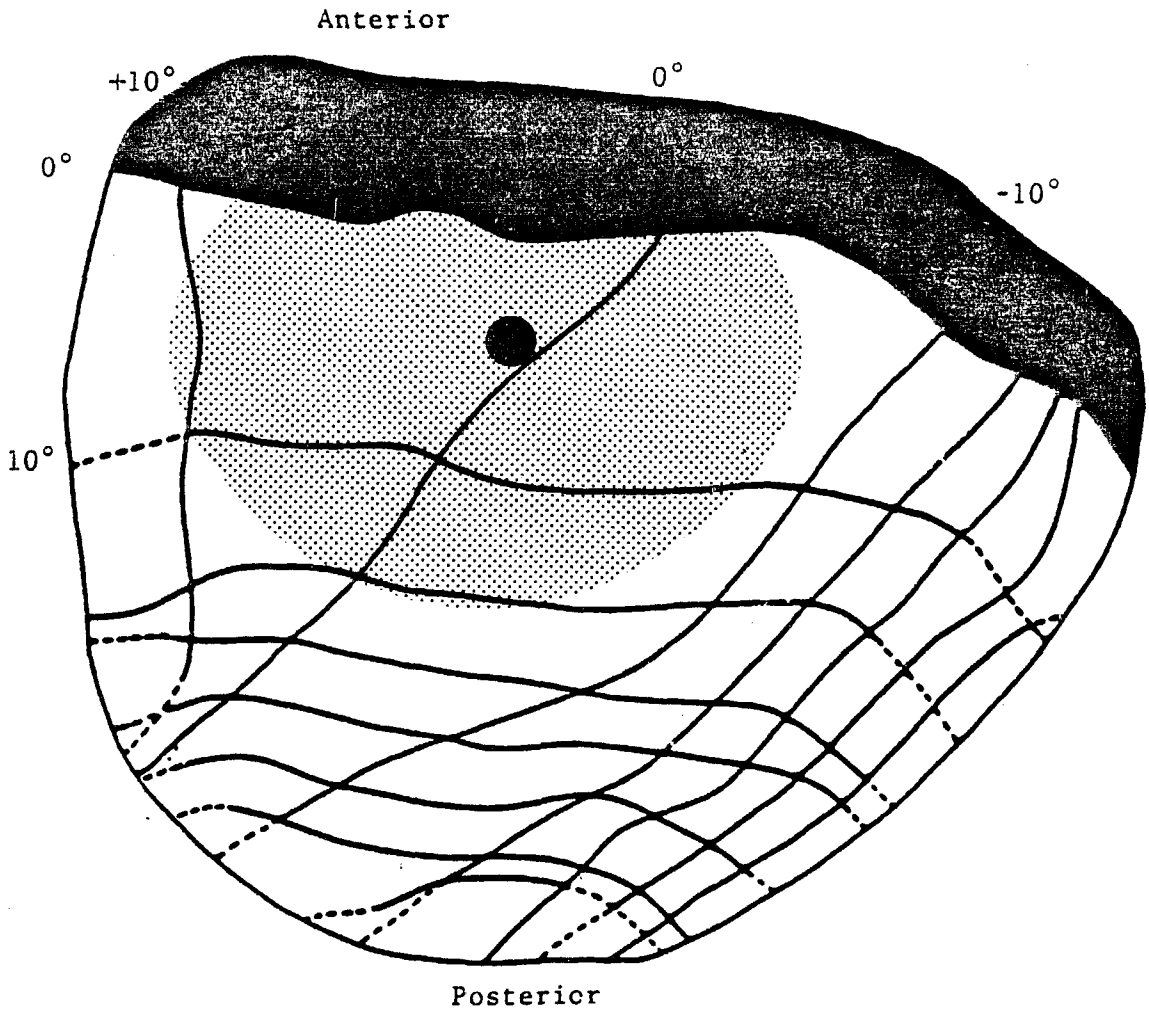

Figure 8. A retinotopic map of the superior colliculus is shown with a representation of collicular lesion #1316 (stippled area) and the position in visual space of the retinotopically matched LGN recording penetration (dot). Horizontal lines represent the vertical meridian and isoazimuth lines. The more nearly vertical lines represent the horizontal meridian and isoelevation lines. The collicular representation of ipsilateral visual space is shown in black. Modified from Feldon, Feldon, and Kruger (1970).

no effect on the relative encounter rates of X and Y cells.

CHAPTER IV
DISCUSSION

The Monocular Paralysis Effect

Previous studies (Garraghty et al., 1982; Guido et al., 1988) indicate that the suppressed X cell encounter rate evident in the LGN of the monocularly paralyzed cat (the monocular paralysis effect) is a manifestation of binocular-visual/proprioceptive integrative processes. The thrust of this study was to investigate the involvement of some extrathalamic structures in these processes.

To test the hypotheses that the cerebellum and/or superior colliculus is/are involved in the maintenance of the monocular paralysis effect, it must first be established that the monocular paralysis effect was manifest at the time the cerebellar or collicular lesion was performed. The monocular paralysis effect is the suppression of X cells recorded under sedated conditions after monocular paralysis, but it is not sufficient to record the X cell encounter rate in the sedated condition because between-animal variation in this measure makes it an unreliable indicator of the monocular paralysis effect. It has been established previously, however, that the monocular paralysis effect is abolished by the induction of anesthesia such that, relative to the sedated condition, there is a reliable increase in the X cell encounter rate when the animal is anesthetized. That is, the monocular paralysis effect is revealed by the induction of anesthesia. The direction of the difference in the X cell encounter rate between the sedated and anesthetized passes (which together constitute the paired-pass) is thus taken to show the presence of the monocular paralysis effect in the sedated condition (Guido et al., 1988; Schroeder et al., 1988). For the present

study, as in these previous studies in which the paired-pass was used to demonstrate the monocular paralysis effect, in the pre-lesion condition the X cell encounter rate of the anesthetized (or, alternatively, ipsilateral visual cortex cool) member of each paired-pass was higher than that of the sedated member of the paired-pass.

In previous studies, the monocular paralysis effect, revealed by anesthesia, has been found to be extremely reliable and robust, evident in every paired-pass attempted (Guido et al., 1988; Moore et al., 1988; Schroeder et al., 1988). This was also the case in the present study, thus providing a solid reliable background for determining the effects of the cerebellar and collicular lesions.

Cerebellar Involvement in the Monocular Paralysis Effect

The finding that the cerebellar lesion returned the X cell encounter rate from the depressed values typical of monocularly paralyzed cats to values similar to those obtained for the anesthetized member of the paired-pass indicates that the cerebellum is part of an extraretinal-extrathalamic circuit supporting the maintenance of the monocular paralysis effect. This interpretation rests on two assertions which are evaluated below: 1) that the changes in the X cell encounter rate are "real" and are not a result of sampling error and 2) alternate hypotheses regarding the cause of the reversal of the X cell encounter rate as measured after the cerebellar lesions can be refuted.

Sampling error. The presence of the monocular paralysis effect in each cat, as demonstrated by the higher X cell encounter rate in the anesthesia (or, alternatively, ipsilateral visual cortex cool) member of the paired-pass, provides a very reliable background against which the increase in the X cell encounter rate (relative to the sedated pass) can be detected after the cerebellar lesion. However, two potential sources of sampling error should be discussed. First, each X cell encounter rate measurement of each cat in each pre-lesion and post-

lesion condition was based on a single recording penetration through the LGN from which a sample of cells was obtained. Therefore, sampling error (of cells within the LGN) could result in erroneous estimates of the X cell encounter rate for a particular recording pass, especially if the size of the cell sample was small. Second, the number of animals used to demonstrate the effect of the cerebellar lesion was small (four) thus increasing the likelihood that an unrepresentative sample might be used to evaluate the effects of the cerebellar lesion.

If these potential sources of sampling error could account for the present results one would expect to see a great deal of variance between estimates of the X cell encounter rate change between conditions of the paired-pass for each cat. However, even though the cell sample size varied between passes, estimates of this X cell encounter rate change did not vary greatly and the direction of change never varied. Indeed, of the 49 cats in which the monocular paralysis effect has been measured by the paired-pass methodology (Guido et al., 1988; Moore et al., 1988; Schroeder et al., 1988) all have shown depressed X cell encounter rates which could be increased in single paired penetrations by imposing surgical levels of anesthesia- the same methodology we used to verify the monocular paralysis effect in each of the animals used in the present experiment. Similarly, the increase in the encounter rate for X cells after the cerebellar lesions was noted in every cat tested thus virtually ruling out the possibility that mere sampling error can account for the results in spite of the small number of cells and cats sampled.

Alternate hypotheses. Hypotheses inconsistent with our interpretation of the increase in the X cell encounter rate after the cerebellar lesion, but also ostensibly consistent with the data, also exist and must be ruled out if we are to conclude that the cerebellum is actually part of an extraretinal, extrathalamic

circuit which is involved in the maintenance of the monocular paralysis effect. These other interpretations of the increase in the X cell encounter rate noted after the cerebellar lesion include: the possibility of brainstem damage incurred during surgery, the possibility that the animal was not allowed adequate recovery from anesthesia, residual effects of anesthesia, and general surgical trauma.

It is possible that aspiration of brainstem tissue occurred as a result of the cerebellar lesion and that this change in the input from brainstem structures (such as the brainstem reticular formation which, as noted in the Introduction, may differentially innervate X and Y cells in the LGN) may have been responsible for the increased rate noted after the cerebellar lesion. This interpretation can be fairly easily refuted by the photographic representations of the lesions. As noted in the Results, a much more extensive lesion would have been necessary to damage the underlying pons or adjacent structures.

The possibility that the cerebellar lesion compromised the blood supply to areas of the brainstem that were crucial in maintaining the monocular paralysis effect must also be addressed. To this end, there are three questions about the vascularization of the brainstem that should be discussed: 1) Could the lesion of the cerebellum and the requisite destruction of that portion of the vasculature interfere with the arterial blood supply of other areas of the brain including but not limited to midbrain, pons, and medulla? This supposition is not possible since, in both hemispheres, the cerebellum and the rest of the brainstem are supplied by separate branches of a single main artery (Netter, 1983). (Logically it is possible that the blood supply to the visual cortex could have been compromised as well, but the vascularization of the visual cortex and cerebellum are well separated; Netter, 1983). 2) Could the surgical removal of part of the cerebellum have resulted in a blockage of the veins that drain the

rest of the brainstem? Though the same vein drains the superior aspect of the cerebellum and part of the brainstem, the cerebellum is distal to the brainstem (on this vein) and therefore a cerebellar lesion could not result in reduced drainage of the brainstem. 3) Could the extravasation of blood incurred during the surgery have resulted in subdural hematoma thus causing intracranial pressure near structures in the brainstem critical for the maintenance of the monocular paralysis effect or destruction of neural tissue there as a result of the toxic effects of blood? No subdural blood in the area of the brainstem was found upon inspection of the brains once they had been removed from the skull. Additionally, an argument against each of these possibilities is that any damage large enough to have resulted in diminished function of the brainstem would likely have caused the death of at least some of the cats. All of the cats in this study were sacrificed by the experimenter when recording was completed. In summary, it is unlikely that the cerebellar lesions compromised the blood supply to other areas of the brain or resulted in blood leakage to other parts of the brainstem.

Another possible interpretation of the increase in the X cell encounter rate noted after the cerebellar lesions is that the animal might not have recovered from the effects of the surgical anesthesia induced to perform the cerebellar lesion. However, arousal state of animal was assessed frequently before and during recording in the post-operative lesion condition and was maintained in the sedated condition. Therefore, the enhanced X cell encounter rate was not due to deep surgical anesthesia, to which the monocular paralysis effect is known to be sensitive.

It is also reasonable to hypothesize that the enhanced X cell encounter rate was due to some residual effect of the anesthesia that the monocular paralysis effect may be sensitive to but which may not be manifested as a classical

behavioral sign of anesthesia. This conjecture is not impossible since it is known that anesthesia is not a unitary process and that behavioral signs of anesthesia that are usually present together can be dissociated if localized structures of the brain are anesthetized. However, this is not a likely cause of the increased X cell encounter rate we observed since if there were any residual effects of anesthesia they would have also occurred in animals which were anesthetized in preparation for control visual cortex (contralateral to the recorded LGN) ablation experiments (Moore et al., 1988) which had no effect on X cell encounter rates.

It could also be speculated that general surgical trauma was somehow responsible for the increased X cell encounter rate after the cerebellar lesions. There are four ways in which surgical trauma could be hypothesized to have contributed to the cerebellar lesion results: 1) physiological shock due to blood loss, 2) mechanical disruption of unlesioned neural tissue as a consequence of removal of the target area, and 3) axotomies of projections from the LGN or other parts of the monocular paralysis circuit.

Blood loss incurred during the surgical procedure may have resulted in shock and perhaps mimicked some aspect of the anesthetized condition in some crucial way. It is, however, unlikely that this could account for the present results because if physiological shock could cause an increase in the X cell encounter rate then it would have done so in the control (contralateral) visual cortex ablation experiments, which it did not (Moore et al., 1988). This assertion can be made since similar amounts of brain tissue and blood were removed in the two surgeries (and as a consequence the body weight to blood volume ratio was approximately the same after cerebellar lesions and contralateral visual cortex lesions). Therefore it is probably the case that

physiological shock can not account for the increase in the X cell encounter rate noted after the cerebellar lesion.

General mechanical trauma incurred as a result of the aspiration procedure could also be hypothesized to cause the increase in the X cell encounter rate noted after the cerebellar lesion. However, aspiration was also used in the removal of the contralateral visual cortex (Moore et al., 1988), which had no effect on the X cell encounter rate, and similar amounts of tissue were taken in the cerebellar lesion and visual cortex surgeries. Therefore mechanical trauma is unlikely to have caused the present results.

It could also be hypothesized that axotomies (as a result of the cerebellar lesions) were made of geniculate projections to the cerebellum. This hypothesis can easily be refuted since there are no direct projections of the LGN to the cerebellum (Gould, 1980). However, a general "diaschisis" could result from the lesion of a large structure in the brain which could be hypothesized to cause the X cell encounter rate increase noted after the cerebellar lesion. It is unlikely that the cerebellar lesion caused any more such diaschisis than the control visual cortex lesions (Moore et al., 1988) which again did not result in an increase in the X cell encounter rate and therefore it is unlikely that the general effect of massed axotomies can account for the present results.

In summary, the effect of cerebellar lesion was not due to unintentional lesion of the underlying brainstem, failure to record the X cell encounter rate in the sedated state, any putative residual effects of anesthesia, or general surgical trauma. Taken together the above evidence supports the notion that the cerebellar lesions, which increased the X cell encounter rate in monocularly paralyzed cats, did so by destruction of neural tissue, restricted to the cerebellum, which in the pre-operative condition was necessary for the maintenance of the monocular paralysis effect.

Collicular Involvement in the Monocular Paralysis Effect

An analysis of the results indicates that the hypothesized role for the superior colliculus in the monocular paralysis effect may be rejected. This failure to reject the null hypothesis can be stated so strongly because the X cell encounter rate increase evident in the pre-lesion anesthesia condition relative to the pre-lesion sedated condition was not present in a single animal in the post-collicular lesion condition. As with the interpretation of the cerebellar lesion results, the interpretation of the results of the collicular lesion condition rests on two points that will be discussed below: 1) it is very unlikely that these data are a result of sampling error and 2) alternative, non-statistical, explanations of the failure to see an X cell encounter rate increase after the collicular lesion can be successfully refuted.

Sampling error. The arguments against a sampling error explanation of the collicular lesion data are similar to those presented for the cerebellar lesion data. First, it is evident from visual inspection that the variability of the estimations of the minimal X cell encounter rate change between the pre-lesion sedated condition and the collicular lesion condition was no greater than that found in the cerebellar lesion cats thus emphasizing that random variability is unlikely to have been responsible for the outcome. Secondly, of the four cats, which all showed the increase in the X cell encounter rate in the anesthetized/visual cortex cool member of the paired-pass, none showed an increase in the X cell encounter rate after the collicular lesion. It is unlikely that this degree of consistency could be the result of sampling error particularly in light of the relevant history of the monocular paralysis effect described in the section on cerebellar lesions.

Alternate explanations. Given that these data are reliable in a statistical sense, it remains to be determined whether or not the failure to get a reversal

of the monocular paralysis effect with the collicular lesion was due to flawed procedures that resulted in inadequate lesions of the superior colliculus. There are two types of errors that could have been made during the lesioning procedure: 1) the lesions may have been incorrectly placed and 2) the lesions may have been insufficiently large.

First of all it could be hypothesized that the electrolytic lesions were incorrectly placed and therefore did not destroy the area in the superior colliculus retinotopically matched to LGN penetrations. Reconstructions of the lesion sites are, in one case, at variance with some published retinotopic maps of the superior colliculus (Berman & Cynader, 1972; Kruger et al., 1970). However, since, as explained in the Results, the lesions were placed using physiological criteria, variability between animals in the representation of visual space in the superior colliculus more easily explains the this discrepancy. In any case, even in those instances where the physiological and anatomical evidence converge there was no increase in the X cell encounter rate relative to the sedated condition. Taken together the evidence suggests that the failure to reject the null hypothesis was not due to inaccuracies in the lesion placement.

A "mass action" effect is not ruled out by the accuracy of the lesions. That is, the combined output of a large area of the colliculus could be responsible for the inhibition of X cells and, therefore, small lesions, however accurate, would not reverse this effect. Arguing against this explanation is the large size of the lesions (shown in the Results and in Appendices C and D), making it improbable that a mass action effect was missed.

The arguments presented above strongly suggest that lesions of the superior colliculus do not result in an increase in the X cell encounter rate in the monocularly paralyzed cat. That is, not only did these lesions fail to reverse the monocular paralysis effect, but, given the accuracy of their placement and

their size, it would seem that any lesion of the superior colliculus would have no effect. Thus it would seem that the structural integrity of the superior colliculus is not necessary for the maintenance of the monocular paralysis effect.

Cerebellar Involvement in the Monocular Paralysis Effect- Anatomical and Physiological Considerations

Since the monocular paralysis effect has been shown to rely on the functional integrity of the cerebellum, an examination of the possible cerebellar inputs to the LGN and their effect on relay cells is necessary. There are no direct projections from the cerebellum to the LGN, however. Instead, as briefly outlined in the Introduction, the cerebellum projects to various structures in the brainstem which in turn richly innervate the LGN. These brainstem structures have been shown to exert powerful modulatory influences on the LGN and could therefore provide a functional link by which the cerebellum may influence geniculate processing of visual information. Once these pathways have been described in more detail a discussion of the specific effects they may have on the LGN will be undertaken. The goal of this discussion obviously will be to explain how the decrease in the encounter rate of X cells (thought to reflect the simultaneous reduction in excitability of X cells as measured by threshold chiasm stimulation and a similarly measured increase in excitability of Y cells [Schroeder et al., 1988]) that results from monocular paralysis could be produced by input from the brainstem. The discussion will, to a large degree, rest on the findings of studies in which the effects of brainstem stimulation (or, alternatively, direct application of neurotransmitters) on the LGN are investigated.

The reversal of the monocular paralysis effect by induction of anesthesia serves as a model of the reversal by cerebellar lesion since the effect of anesthesia on the brainstem reticular formation (by which the cerebellum has

its effect on the LGN) is, to some degree, known. If it is possible to explain the monocular paralysis effect in terms of these brainstem influences on the LGN, then, given the cerebellum's connections to these same brainstem areas, it may be hypothesized that the reversal of the monocular paralysis effect in the post-cerebellar lesion condition is the result of the loss of input from the cerebellum to these brainstem areas.

The difficulty of explaining completely the effects of monocular paralysis in terms of studies which show brainstem's modulatory influence on the transmission of visual information through X and/or Y cells is a direct consequence of the fact that none of the studies that have investigated the effects of brainstem stimulation duplicate the specific set of conditions necessary to demonstrate the monocular paralysis effect. Specifically, the monocular paralysis effect has been found to operate on a cell type by eccentricity by anesthesia basis (Garraghty et al., 1982; Schroeder et al., 1988; Willis, Salinger, Vaughan, Moore, & Cole, 1988). That is, to investigate the effects of oculomotor manipulations on the relative excitability to visual stimulation of X and Y in monocular paralysis cells one must simultaneously be attentive not only to whether the particular cell under study is an X or Y cell, but also to the eccentricity of the cell's receptive field (effects are much weaker in the more peripheral receptive field locations and may even reverse in sign; Willis, unpublished observations; Willis et al., 1988) and to the anesthesia state of the animal (since surgical anesthesia has been found to increase the X cell encounter rate above that of the typically low values of the sedated monocular paralysis preparation; Garraghty et al., 1982; Guido et al., 1988; Schroeder et al., 1988). Of the papers to be reviewed which concern themselves with the effects of brainstem stimulation on the LGN, none control for all of these parameters which together define the conditions of the monocular paralysis

effect. Interpretations of data derived in physiological experiments without this control may therefore be of limited value in developing an understanding of monocular paralysis. That is, brainstem stimulation experiments reviewed here may yield clues only about the involvement of the brainstem reticular formation in the monocular paralysis effect, but not precise information about the sign of influence on X and Y cells or even about absence of effect.

After establishing that there are significant inputs from the cerebellum to the to the LGN via the brainstem reticular formation a discussion of the effects of stimulation of these brainstem areas will follow.

Cerebellar input to brainstem. Of the three cerebellar nuclei (fastigial, interpositus, and dentate) that provide output from the cerebellum, only the fastigial (or medial) nucleus projects significantly to the brainstem structures implicated in the modulation of LGN activity and receives input from the visual-proprioceptive areas of the cerebellum (lobules V-VII). The fastigial nucleus projects to three brainstem structures the stimulation of which affects geniculate processing: the raphe nucleus (Asanuma et al., 1983), the locus coeruleus (Snider, 1975), and portions of the pontomesencephalic reticular formation (PMRF; Walberg et al. 1962). Thus the cerebellum could produce an effect in the LGN via these brainstem nuclei.

The vestibular nuclear complex is another, separate output from the cerebellum, particularly from the flocculus, nodulus, and uvula (Angaut & Brodal, 1972). The vestibular nuclei project to the reticular formation and therefore provide another route by which the cerebellum may influence the LGN.

In summary, the only fairly direct routes by which the cerebellum may influence the LGN through the brainstem is by the raphe nucleus, the locus coeruleus, and PMRF which receive projections from cerebellar lobules V-VII via

the fastigial nucleus and perhaps, again, through the PMRF which receives information from the cerebellum via the vestibular nuclei.

Brainstem mediated cerebellar input to the LGN. The brainstem structures identified above have direct inputs to the LGN and have been shown to affect the activity of relay cells in ways consistent with a role in the monocular paralysis effect. Of the three main brainstem inputs to the LGN, the locus coeruleus and raphe nucleus, are well defined and are associated with a particular neurotransmitter. The PMRF is less well defined and its connectivity to the cerebellum and LGN is more complicated.

It is relevant to the study of the monocular paralysis effect, which is binocular in nature, that not only is the brainstem reticular formation innervation of the LGN bilateral, but at least part of the input is bilaminar and is thus binocular. Thus, a change in the innervation of the LGN by the brainstem reticular formation (perhaps resulting from changes in the cerebellum that may occur as a result of monocular paralysis) may result in changes in the relative encounter rates of X and Y cells in both A and A1 and would therefore would be binocular.

The locus coeruleus projects directly to the LGN/perigeniculate complex (Pasquier & Villar, 1982) and there is some fairly direct evidence, in addition to demonstrations of anatomical connectivity, that the cerebellum could modulate activity in the LGN via this noradrenergic pathway. Unilateral lesions of the vermal cortex, plus the fastigial nucleus, lead to a decrease in the level of noradrenaline in the ipsilateral cerebral cortex of rats (Snider & Snider, 1977), whereas kainic acid lesions of the vermal cortex alone cause a substantial increase in the noradrenaline concentration in the ipsilateral forebrain, perhaps by disinhibition of fastigial neurons (Snider & Snider, 1979). It seems reasonable to imagine then that lesions of the cerebellum which include the

fastigial nucleus would probably result in a decrease in the release of noradrenaline from locus coeruleus neurons to the LGN as well. It should be noted that the fastigial nucleus has input from lobules V-VII (rats; Armstrong & Schild, 1978) which, as reviewed in the Introduction, are sensitive to visual and extraocular muscle proprioceptive information. Thus, activity in these areas related to proprioceptive information from the eyes could affect the relative encounter rate of X and Y cells in the LGN through the locus coeruleus.

It seems then that anatomical pathways exist by which the locus coeruleus could affect LGN processing. Furthermore, the cerebellum appears to have significant input to the locus coeruleus and has been shown to effectively modulate its activity. Thus, cerebellar lesions could affect the activity of the LGN by modifying the input to the locus coeruleus.

Modulation of LGN activity by the cerebellum could also be mediated by the dorsal raphe nucleus which has been shown to project to the LGN (Pasquier & Villar, 1982) and whose stimulation has been shown to affect the excitability of relay cells in the LGN (Foote, Maciewiez, Mordes, 1974; Foote, Mordes, Colby, & Harrison, 1977). There may a differential innervation of the LGN by the dorsal raphe since Mize and Payne (1987) have found that lamina A and A1 exhibits a lower innervation density of serotonergic fibers that the C lamina, but the physiological implications of this finding are not known. There is also a projection to the perigeniculate nucleus from the raphe nucleus (Ahlsen & Lo, 1982) which could mediate geniculate effects. Therefore the dorsal raphe, which has been shown to receive input from the cerebellum, has direct input to the LGN and could therefore mediate the cerebellar influence on the LGN.

In addition to serotonergic (from the dorsal raphe nucleus) and noradrenergic (from the locus coeruleus) input to the LGN, cholinergic input to the LGN (de Lima, Montero, & Singer, 1985; de Lima & Singer, 1987; Stichel &

Singer, 1985) and its modulatory effect on the activity of geniculate neurons (Ahlsen, Lindstrom, & Lo, 1984; Eysel, Pape, & Schayck, 1986; Francesconi, Muller, & Singer, 1988; Sillito, Kemp, & Berardi, 1983) are well known. Therefore it seems reasonable to hypothesize that the cholinergic influence on the LGN may be involved in the monocular paralysis effect. The cell bodies of the cholinergic neurons which project to the LGN can be found in the general area of the PMRF, mostly in the parabrachial nucleus (Ahlsen & Lo, 1982; Hughes & Mullikin, 1984; Kimura, McGeer, Peng, McGeer, 1981). No cerebellar projection to the parabrachial nucleus has been described, but there are projections from the cerebellum to other areas of the PMRF (described above) and it is through these reticular nuclei that the cerebellum may influence the activity of the parabrachial nucleus and, thus, the LGN.

As evidence that reticular nuclei that have no direct projection to the LGN may still influence geniculate activity, Ahlsen et al. (1984) have shown that discrete stimulation within an extremely large area of the brainstem has an effect on the transmission of information through the LGN. Since many of these areas of the brainstem do not project directly to the LGN it seems reasonable to assume that they are producing their effects via reticular nuclei that do project to the LGN, the parabrachial nucleus perhaps among them. Therefore, in addition to reviewing noradrenergic and serotonergic systems, cholinergic influences on the LGN via the parabrachial nucleus shall also be reviewed, even though there seems to be no direct anatomical linkage between the cerebellum and the LGN via cholinergic fibers.

Physiological Effects of Brainstem Reticular Formation Stimulation

The stimulation of the brainstem reticular formation may logically have several different types of influences on the excitability of X and Y cells, each with its own implications for a possible role in the monocular paralysis effect.

However, since the MP effect is revealed through measurements of the relative encounter rates of X and Y cells and not relative excitability of X and Y cells, these implications rest on the assumption that excitability of geniculate neurons contributes significantly to encounter rates of X and Y cells. This assumption is given some support from data which show that, congruent with its effect of increasing the encounter rate of X cells in monocularly paralyzed animals, anesthesia increases the excitability in 73% of X cells and decreased excitability in 55% of Y cells (Schroeder et al., 1988). Therefore, it is not unreasonable to suggest that the encounter rate for X cells reflects the excitability of relay cells in the LGN.

First, stimulation of a particular brainstem area in an anesthetized physiological preparation could mimic the effects of increased arousal (perhaps comparable to our sedated condition) relative to the anesthetized condition, and thus may cause an increased excitability of Y cells. This increased excitability of Y cells may result in an increased encounter rate of Y cells (Schroeder et al., 1988) such as that noted in the pre-lesion sedated condition of the present experiment. Secondly, stimulation of brainstem may have a differential effect on the excitability of X and Y cells, but not in the direction predicted by Schroeder et al. (1988). This possibility could suggest that the stimulated areas may be involved in the monocular paralysis effect, but that other factors to which measures of oculomotor manipulations are sensitive [anesthesia (Schroeder et al., 1988; retinal eccentricity (Willis et al., 1988; Willis, unpublished observations)] were not controlled for and therefore resulted in a reversal of the sign of the stimulation effects. Third, stimulation of some brainstem areas or with particular neurotransmitters may have similar effects on X and Y cells. Again, anesthesia, eccentricity, and/or oculomotor status may have concealed a differential effect consistent with the monocular paralysis

effect. Fourth and last, stimulation of some areas of the brainstem will obviously have no effect on the excitability of X and Y cells.

Discussion of the effects of brainstem reticular formation stimulation will be divided into three sections corresponding to three possible routes by which brainstem stimulation may produce its various effects on relay cells: modulation of cells of the perigeniculate nucleus which serve as interneurons of the LGN, modulation of intrageniculate interneurons, and direct influence on relay cells of the LGN. Guided by anatomical studies of cerebellar connections to brainstem areas which in turn project to the LGN (considered above), experiments involving the investigation of effects on LGN of stimulation of the locus coeruleus, raphe nucleus, and parabrachial nucleus will be considered.

Perigeniculate neurons. The argument that, under cerebellar control, brainstem modulation of perigeniculate neurons could produce the reduction in the encounter rate for X cells that characterizes the monocular paralysis effect has two parts: 1) a modulation of perigeniculate cells may alter the excitability of X and Y cells and thus change the relative X cell encounter rate and 2) modulation of the perigeniculate by the brainstem does occur. A discussion of these two aspects of this argument follows.

The perigeniculate may provide differential input to X and Y cells in the LGN and thus may differentially inhibit these two classes of relay cells. There are two types of inhibition acting on relay cells (Dubin & Cleland, 1977): 1) inhibition supplied by the perigeniculate, termed recurrent because it is driven by collaterals of LGN relay cells and 2) inhibition supplied by the intrageniculate interneurons, termed feedforward because the inhibitory neurons receive direct innervation from retinal ganglion cells, which will be discussed in the next section. The perigeniculate, lying just dorsal to the LGN, receives excitatory input from collaterals of relay cells in the LGN (Ahlsen, Lindstrom, &

Lo, 1983; Dubin & Cleland, 1977) and in turn projects back to the LGN making GABA-ergic inhibitory synaptic contact with relay cells (Lindstrom, 1982; Montero & Scott, 1981; Montero & Singer, 1984). Since perigeniculate neurons possess binocular receptive fields, their input to LGN relay cells may, in part, account for binocular aspect of the monocular paralysis effect. Physiological evidence suggests that recurrent inhibition is evident in both X and Y cells more or less equally (Lindstrom, 1982). If it were always the case that the relative amount of recurrent inhibition on X and Y cells is equal and independent of factors such as eccentricity and anesthesia then, an analysis of the brainstem inputs to the perigeniculate would be unnecessary since the monocular paralysis effect must be the result of processes which differentially affect X and Y cells. However, we do not have enough evidence to conclude that perigeniculate inhibition of relay cells is independent of anesthesia and eccentricity because these factors were not manipulated in the cited studies.

There is anatomical evidence which suggests that the inhibitory influence of the perigeniculate nucleus is felt more keenly by Y cells than X cells. Inhibitory synaptic contact on relay cells take two forms, F1 and F2 (Singer, 1977). F1 synapses, which derive from the perigeniculate and are the anatomical substrate of recurrent inhibition (Montero & Scott; 1981; O'Hara, Sefton, Lieberman, 1980), have been found to predominate on Y cells (Wilson, Friedlander, & Sherman, 1984). This suggests that current physiological estimates of the relative perigeniculate inhibition on X and Y cells, based on data from anesthetized and systemically paralyzed animals and taken without regard for such key factors as retinal eccentricity, may not be entirely accurate and, under different recording conditions, perhaps those under which the monocular paralysis effect can be demonstrated, there may be greater recurrent inhibition of Y cells, as the morphological data suggest.

There is ample evidence to suggest that the brainstem reticular formation (at least the locus coeruleus and parabrachial nucleus) provides modulatory input to the perigeniculate. Shock stimulation of the locus coeruleus activates all perigeniculate cells encountered (Kayama, Negi, Sugitani, & Iwama, 1982) which would increase their inhibition of relay cells. This may have the effect of suppressing Y cells during periods of high locus coeruleus activity since the activation of recurrent inhibition, supplied by the perigeniculate, may, as suggested by the anatomical data (Wilson et al., 1984) impact primarily on Y cells. This suggests that during our sedated condition (which would imply greater locus coeruleus activity relative to the anesthetized condition) a greater amount of Y cell inhibition would occur. This inference seems inconsistent with our data, but such an inference cannot be drawn without systematic manipulation of the anesthesia level and eccentricity of receptive fields of the perigeniculate cells recorded from during the locus coeruleus stimulation.

Perigeniculate cells also receive numerous contacts from cholinergic fibers, probably from the parabrachial nucleus, a single axon making several en passant synapses with a single cell, suggesting cholinergic control of recurrent inhibition (de Lima et al., 1985; de Lima & Singer, 1987; Stichel & Singer, 1985). Eysel et al. (1986) noted an inhibition of LGN cells which acted over a much larger area than the classic surround inhibition of LGN receptive fields which could be disinhibited by the application of ACh. This "long-range" lateral inhibition, which mediated influences from more than 10° outside the receptive field center (at an eccentricity of 10°), could be blocked by bicuculline (indicating it was interneuronal in nature), but could not be blocked by cortical cooling. Based on this information the authors concluded that this type of inhibition was mediated by the perigeniculate (and not the intrageniculate interneurons, which are also GABA-ergic) because of the much greater spread of

terminals of perigeniculate cells within the LGN (Uhlrich, Cucchiaro, & Sherman, 1987). Since cholinergic stimulation has been shown to affect perigeniculate cells (which may preferentially innervate Y cells) then it could be suggested that long-range lateral inhibition underlies the monocular paralysis effect. However, since long-range lateral inhibition is not blocked by cortical cooling, the fact that the monocular paralysis effect can be reversed by cortical cooling (Moore et al., 1988) suggests that these two phenomena derive from different mechanisms.

Parabrachial nucleus (cholinergic) stimulation and iontophoresis of acetylcholine into the perigeniculate completely suppress the resting discharge of most perigeniculate cells (Eysel et al., 1986; Francesconi et al., 1988; Sillito et al., 1983), an inhibition resulting from post-synaptic hyperpolarization (Ahlsen et al., 1984). This would have the effect of reducing the inhibitory effect that perigeniculate cells seem to exert upon the LGN (Eysel et al., 1986). Again, if perigeniculate cells preferentially innervate Y cells (as suggested by the anatomy; Wilson et al., 1984) then a general suppression of perigeniculate neurons could differentially affect the X cell encounter rate. In general, because perigeniculate activity inhibits LGN Y cells the inhibitory effect on perigeniculate cells during parabrachial nucleus stimulation (which may emulate the aroused condition) is consistent with a more general finding that transmission through the LGN is facilitated in the alert awake animal as compared to the drowsy state or slow wave sleep (Singer, 1977; Burke & Cole, 1978; in Ahlsen et al., 1984). More relevant for the present study is the idea that a release of Y cells from perigeniculate inhibition, resulting from the fact that the perigeniculate is itself inhibited by activity in the parabrachial nucleus, could help to explain the higher encounter rate of Y cells (and reduced encounter rate for X cells) in the pre-lesion sedated condition.

If the suppression of the perigeniculate is to explain successfully the monocular paralysis effect, then, assuming that encounter rates are causally related to excitability, not only must the excitation of Y cells be explained, but the concomitant inhibition of X cells must also be accounted for. The inhibition of X cells may be explained by the fact that perigeniculate cells, in addition to inhibiting mostly Y relay cells, also inhibit intrageniculate interneurons (Ahlsen, Lindstrom, & Lo, 1985), which in turn, may preferentially inhibit X cells (Wilson et al., 1984). In this view, if the intrageniculate interneurons are relatively excited (as by parabrachial nucleus activity induced by direct stimulation or, as in the present experiment, sedation relative to deep anesthesia), then X cells should be subjected to increased inhibitory influences and thus would become less excitable to visual or electrical stimulation, as required for the observed effects in the monocular paralysis preparation. Conversely, anesthesia could serve to reduce activity in the parabrachial nucleus thus releasing perigeniculate cells from inhibition which would in turn then inhibit Y cells. In this way induction of anesthesia in the monocular paralysis preparation could result in a decrease in the encounter rate of Y cells.

In summary, acetylcholine application and parabrachial stimulation may explain how a change in input to the parabrachial nucleus, perhaps initiated from the cerebellum, could cause a reduction in the X cell encounter rate of monocularly paralyzed cats. Experimental support for this hypothesis might be obtained through pharmacological blockade of cholinergic input to the parabrachial nucleus which, hypothetically, would enable one to reverse the monocular paralysis effect just as general anesthesia or cerebellar lesion do. Application of scopolamine (a cholinergic muscarinic antagonist) to the area of the perigeniculate retinotopically matched to the recording penetration through the LGN would release perigeniculate cells from inhibition which would then

inhibit Y cells. The concomitant inhibition of intrageniculate interneurons would then presumably release X cells from inhibition thus increasing the X cell encounter rate. Such a shift in the X cell encounter rate would be good evidence that the parabrachial nucleus is involved in the monocular paralysis effect.

It should be pointed out that apparently paradoxical effects of brainstem stimulation can occur with manipulations of anesthesia. Repeated stimulation of the parabrachial nucleus under light halothane anesthesia can facilitate rather than inhibit perigeniculate cell activity. This is likely to occur because increased excitatory input to the perigeniculate cells from corticofugal and geniculocortical fibers resulting from parabrachial nucleus stimulation may outweigh the direct inhibitory action of reticular afferents (Francesconi et al., 1988). This finding underscores the need for attention to anesthesia level in experiments on the LGN and the degree of complexity of the interactions that may take place between the various excitatory and inhibitory influences on the LGN.

Intrageniculate interneurons. Just as with the perigeniculate, the argument that brainstem modulation of intrageniculate interneurons could produce the monocular paralysis effect has two parts: 1) direct brainstem modulation of intrageniculate interneurons may change the X cell encounter rate and 2) modulation of intrageniculate interneurons by the brainstem does occur. A discussion of these two aspects of this argument follows.

Intrageniculate interneurons may provide differential input to X and Y cells in the LGN and thus may differentially inhibit these two classes of relay cells. Intrageniculate interneurons, which comprise 20-25% of the cells in layers A and A1 (Fitzpatrick, Penny, & Schmechel, 1984; Montero & Zempel, 1985; Weber & Kalil, 1983), are innervated by X retinal ganglion cells only (Hamos,

Van Horn, Raczkowski, Uhlrich, & Sherman, 1985; Raczkowski, personal communication) and therefore are virtually indistinguishable from X type relay cells. However, rather than projecting to cortex as relay cells do, these interneurons make inhibitory synapses (termed feedforward inhibition) with relay cells (Dubin & Cleland, 1977) via F2 GABA-ergic synapses (Montero & Singer, 1985) which appear predominantly on X cells (Wilson et al., 1984) and therefore provide a route by which the brainstem reticular formation could affect the transmission of visual information through X cells independent of Y cells.

In contrast to anatomical evidence (Wilson et al., 1984), physiological evidence suggests that feedforward inhibition (from interneurons) occurs on both X and Y cells (Lindstrom, 1982). If this were the case under all recording conditions (i.e., the relative amount of inhibition on X and Y cells was independent of factors such as eccentricity and anesthesia) then an analysis of the brainstem inputs to the intrageniculate interneurons would be unnecessary since the monocular paralysis effect is the result of processes which differentially affect X and Y cells. However, as was the case for perigeniculate cells, we do not have enough evidence to conclude that intrageniculate interneuron inhibition of relay cells is independent of anesthesia and eccentricity because these factors were not systematically manipulated. This leaves the possibility that current physiological estimates of the relative intrageniculate interneuron inhibition on X and Y cells may not be entirely accurate and, under different recording conditions, perhaps those under which the monocular paralysis effect can be demonstrated, there may be greater feedforward inhibition of X cells, as the morphological data suggests (Wilson et al., 1984).

There is ample evidence to suggest that the brainstem reticular formation (at least the locus coeruleus and parabrachial nucleus) directly modulates intrageniculate interneurons. Shock stimulation of the noradrenergic neurons of the locus coeruleus results in an inhibition of all intrageniculate interneurons encountered (Kayama et al., 1982; Nakai & Takaori, 1974). This effect can be shown to be the result of an α-noradrenergic mechanism (by microiontophoretic application of noradrenaline whose action is blocked only by the α-adrenoreceptor antagonist phentolamine; Kayama et al., 1982; Rogawski & Aghajanian, 1980a,b) whose fiber's source is probably the locus coeruleus (Nakai & Takaori, 1974).

There is also considerable evidence that a cholinergic mechanism, perhaps deriving from the parabrachial nucleus (de Lima & Singer, 1987) influences intrageniculate interneurons. Cholinergic synaptic contacts are made with F2 boutons (derived from intrageniculate interneurons) which are found in synaptic arrangements with the retinal afferent and the geniculate dendrite (and thus are called intraglomerular) which suggests an influence over feedforward inhibition (de Lima et al., 1985). Cholinergic contacts at intraglomerular sites suggests that a very discrete control of retinal influence on geniculate neuron activity is possible. Since intrageniculate interneurons probably innervate multiple relay cells, a more global influence on feedforward inhibition is suggested by the fact that acetylcholine hyperpolarizes intrageniculate interneurons by increasing a membrane potassium conductance mediated through muscarinic receptors (McCormick & Pape, 1988). Also, Ahlsen et al. (1984) found that almost all of the intrageniculate interneurons they encountered were inhibited by stimulation within a large area of the PMRF, though stimulus intensities required to reveal the effect were rather high.

There is some evidence that the effect of acetylcholine application on intrageniculate interneurons may differ with the level of anesthesia. In the studies cited above, cats were deeply anesthetized (20 mg/kg ketamine intramuscularly and 15 mg/kg sodium pentobarbital intravenously [McCormick & Pape, 1988]; 35 mg/kg sodium pentobarbital [Ahlsen et al., 1984]). However, in studies in which a lighter anesthesia was used (75% N_20/25% O_2) an excitatory affect of acetylcholine application on intrageniculate interneurons was found (Sillito et al., 1983). These effects which seem to be sensitive to the level of anesthesia have obvious implications for the monocular paralysis effect which is abolished by anesthesia. More generally, the finding that anesthesia induction may reverse the polarity of effect that brainstem stimulation may have supports the idea that experimental manipulation of anesthesia is necessary if we are to guard against misinterpretation of findings gleaned from experiments on anesthetized animals. On the other hand, ethical considerations make the complete abandonment of anesthesia unpalatable. For the present experiment the fact that a change in the level of anesthesia reverses the sign of brainstem stimulation effects substantiates the claim that the mere fact that a brainstem stimulation experiment does not yield results exactly consistent (in sign) with the results of monocular paralysis does not mean that the area of brainstem stimulated has nothing to do with the monocular paralysis effect. That is, if the anesthesia condition had more nearly matched those used for the sedated condition used in the monocular paralysis experiments the results may have been more consistent.

The inhibition of intrageniculate interneurons by brainstem reticular formation stimulation, which may occur during deep anesthesia, would apparently reduce the amount of feedforward inhibition on X cells thus making X cells easier to stimulate. With lighter levels of anesthesia, perhaps not unlike

our sedated condition, parabrachial nucleus activity may excite intrageniculate interneurons thus making X cells harder to stimulate. These findings are consistent with our data which show a higher X cell encounter rate during deep anesthesia relative to sedation. However, it is not known how the anesthesia effects cited in the above studies would interact with the classical notion that the brainstem reticular formation, including the parabrachial nucleus, is less active under deep anesthesia. That is, even though deep anesthesia somehow causes parabrachial nucleus stimulation to inhibit intrageniculate interneurons and thus increase the excitability of X cells, it is harder to know what the resting activity of the parabrachial nucleus is when not artificially stimulated and how much excitation of X cells would occur under more "normal" circumstances, as with our monocular paralysis preparation.

Relay cells. It is obvious how a direct modulation of relay cells could produce the monocular paralysis effect since the only indication we have that monocular paralysis alters the transmission of visual information through the LGN is that it results in a change in the relative encounter rates of X and Y relay cells. In this regard, in one of the earlier reports of brainstem reticular formation influence on the LGN, stimulation of various areas within the brainstem reticular formation resulted in an excitation of X cells relative to Y cells in the LGN (Foote et al., 1977).

There seem to be two types of effects of brainstem reticular formation stimulation which could result in changes in the response of relay cells to specific visual stimulation or spontaneous firing rate. Changes in the receptive field center excitatory response which do not seem to mediated by disinhibition will be discussed. Changes in the receptive field surround inhibition, produced by modulation of intraglomerular synapses on the relay cell dendrite and by effects on the intrageniculate interneurons, have already been discussed.

There is clear evidence that relay cells are directly affected, perhaps differentially, by brainstem stimulation. The effect of locus coeruleus stimulation on almost all relay cells is a facilitation of spontaneous firing with, in some cases, an early period of suppression (Kayama et al., 1982). Similar results have been obtained using evoked potentials (Nakai & Takaori, 1974). This effect of locus coeruleus stimulation on relay cells seems not to be mediated through perigeniculate or intrageniculate interneurons since picrotoxin (a GABA antagonist which would block both feedforward and recurrent inhibition) does not facilitate the excitation of relay cells deprived of their retinal afferents as noradrenaline does (Rogawski & Aghajanian, 1980a,b). Thus the locus coeruleus probably does not excite LGN relay cells through disinhibition, but rather somehow influences the excitatory response to retinal stimulation directly.

Serotonin (whose major source is the raphe nuclei) has a depressant effect on relay cells in the LGN. Stimulation of the dorsal raphe (Foote et al., 1974) or direct application of serotonin (Marks, Speciale, Cobbey, & Roffwarg, 1987; Rogawski & Aghajanian, 1980c) results in a decrease in the evoked activity of LGN relay cells.

It seems that even though the authors cited above did not make special mention of X and Y cells in the LGN when assessing the effects of locus coeruleus and raphe stimulation it is apparent that the effect of such stimulation was the same for both relay cell types since all of the cells tested showed the same effect. However, this lack of differential effect on X and Y cells does not rule out the possibility that the locus coeruleus or raphe nuclei play a role in the maintenance of the monocular paralysis effect since the anesthesia used or its interaction with eccentricity may distort the effect of their activity on the LGN.

Summary. It has been demonstrated that the brainstem reticular formation (including the dorsal raphe, locus coeruleus, and parabrachial nucleus) have anatomical connections to the LGN and that the activity of these brainstem sites can differentially modulate the excitability of X and Y cells. According to Schroeder et al. (1988), the modulation of the excitability of relay cells could explain the decrease of the encounter rate for X cells relative to Y cells in the LGN which occurs as a result of monocular paralysis. Therefore, brainstem input to the LGN, thought to be controlled, in part, by the cerebellum, is hypothesized to be at least partly responsible for the maintenance of the reduction of the encounter rate for X cells which occurs as a result of monocular paralysis.

The brainstem reticular formation has been shown to modulate activity at each of three locations within the LGN/perigeniculate complex (perigeniculate neurons, intrageniculate interneurons, relay cells). In certain cases (e.g., parabrachial stimulation/acetylcholine application effects on perigeniculate cells and consequential effects on relay cells), the differential effect on X and Y cells has been shown to occur in the direction predicted by anesthesia effects on the X cell encounter rate and activity level of the brainstem reticular formation. In other cases, a modulation of relay cells has been shown, but it was not a differential effect on X and Y cells or it was not in the expected direction. To explain how these effects still might play a part in the monocular paralysis effect it was suggested that the conditions under which these brainstem stimulation data were collected were not the same as those under which the monocular paralysis effect was measured. That is, the monocular paralysis effect has been shown to operate on a cell type by anesthesia level by eccentricity basis and brainstem stimulation experiments have so far failed to systematically investigate the effects of these factors. In support of the claim

that this lack of experimental control has resulted in the apparent disagreement between the monocular paralysis literature and brainstem stimulation literature, a differential effect of parabrachial stimulation on intrageniculate interneurons is found if level of anesthesia is varied (cf Ahlsen et al., 1984; McCormick & Pape, 1988; Sillito et al., 1983). Perhaps an inclusion of the eccentricity factor would yield even more information about the action of these brainstem input on the transmission of visual information through the LGN.

The cerebellum has substantial input to the brainstem sites implicated in the modulation of LGN neurons and the lesion of the cerebellum has been shown to reverse the monocular paralysis effect. Therefore, the cerebellum may, in part, act to control the relative excitability (and thus encounter rate) of X and Y cells through its connections to the brainstem reticular formation.

In the following two sections an analysis will be undertaken of the implications of the similar effect on the encounter rate of X cells in the monocularly paralyzed cat of cerebellar lesions to that of lesions of visual cortex and induction of surgical levels of anesthesia. Finally, a further analysis of the cerebellum's role in the monocular paralysis effect will concentrate on how certain features of the cerebellum might contribute to the monocular paralysis effect and what the role of the cerebellum in the maintenance of the monocular paralysis effect implies about amblyopia and neural plasticity of binocular-visual/proprioceptive integration.

Cortical Influence Over Geniculate Processing

The influence of cortex over geniculate processing, suggested by the massive corticofugal projection to the LGN, has recently been shown to play a part in the monocular paralysis effect. Cryogenic blockade or ablations of visual cortex ipsilateral to the recorded LGN have been shown to reverse the monocular paralysis effect in the LGN just as anesthesia induction and

cerebellar lesions do (Moore et al., 1988). It therefore seems necessary to review the mechanisms by which visual cortex may produce this effect on the LGN and how it may interact with the cerebellar-brainstem portion of the mechanism(s).

Interaction between corticofugal and cerebellar/brainstem influences on the LGN. It is clear that both corticofugal and cerebellar/brainstem projections synapse onto neurons in the LGN/perigeniculate complex. It is therefore possible that the reason the cerebellar and visual cortex lesions have the same effect on the encounter rates of X and Y cells is that there is an interaction between these inputs to which the monocular paralysis effect is sensitive. Cholinergic mechanisms controlling geniculate processing have been shown to interact with the activity level of cortex in a way that might partially explain why cortical lesions reversed the monocular paralysis effect. Francesconi et al. (1988) reported that effects of acetylcholine application on the LGN increased during desynchronization of the cortical EEG (a condition perhaps not unlike our pre-lesion sedated condition). That is reticular stimulation and acetylcholine application increases spontaneous activity in the LGN beyond the activity level of the driving retinal fibers only when the EEG was desynchronized. A similar effect has been noted in the rat (Kayama, Suchitomo, Ogawa, 1986). It appears then that both brainstem and cortical influence work together to control geniculate activity in a fashion which is suggestive of a role in the effect of extrathalamic lesions on the monocular paralysis effect.

One of the more probable explanations of the monocular paralysis effect, mentioned in a previous section, was that the activity in the parabrachial nucleus suppresses the activity of perigeniculate interneurons thus releasing Y cells from inhibition. Also, since perigeniculate neurons inhibit intrageniculate

interneurons, the inhibition of perigeniculate neurons would result in an increase in the activity of intrageniculate interneurons thus suppressing the activity of X cells. It is not known if the interaction of cholinergic input with the activity level of the cortex (Francesconi et al., 1988) occurs at synapses on perigeniculate neurons. If it does then this would explain why the lesion of cortex increased the encounter rate of X cells despite the sedated levels of anesthesia (and, presumably, a relatively high activity level of the parabrachial nucleus) and an intact cerebellum. It is presently not understood how this interaction between cortical activity and the effects of cholinergic input into the LGN are related to the role cortex play in suppressing diplopic images (described below).

Another way in which visual cortex could reverse the monocular paralysis effect is that the loss of input to the brainstem reticular formation from cortex could produce an anesthesia-like condition. This role for cortex in the monocular paralysis effect is less interesting in that it doesn't involve its binocular visual input to LGN, but is plausible nonetheless.

Sherman and Koch (1986) propose that at least one function of visual cortex is to prevent low threshold spike "de-inactivation." The low threshold spike is a highly non-linear response mode of relay cells caused by a Ca^{2+} conductance which can only be de-inactivated by prolonged (> 100 msec) hyperpolarization of relay cells. There are several processes that might cause this hyperpolarization including GABAergic inputs, cholinergic inputs, and inactivity of the corticofugal pathway (whose activity directly depolarizes relay cells). Thus, the lesion of cortex or, perhaps anesthesia, may reduce corticofugal input to the LGN thus allowing relay cells to hyperpolarize and produce the low threshold spike when next stimulated.

This proposed purpose for the corticofugal projection is not an attractive hypothesis for two reasons. First it is unlikely that such a intricate system of inhibitory and facilitatory inputs (Schmielau & Singer, 1977; Tsumoto et al., 1978) would only have the purpose of producing a tonic depolarization in the LGN to permit the more or less faithful transmission of visual signals to the cortex. Secondly it is not at all clear how the "bursty" firing pattern of the low threshold spike would be related to the inhibition (and silencing) of X cells in monocular paralysis. Therefore it is unlikely that the low threshold spike plays a role in monocular paralysis.

Binocular input to the LGN from visual cortex. The discovery that the corticofugal input to the LGN is binocular (Harvey, 1978; 1980; Tsumoto et al., 1978; Tsumoto & Suda, 1980) certainly suggests a role for this projection in binocular integration. Indeed, the influence of this projection on the activity of relay cells seems to be inhibitory or excitatory depending on whether the separation of the receptive field centers of the geniculate and cortical cells exceed approximately 3.1° or are less than 2.3°, respectively (Schmielau & Singer, 1977; Tsumoto et al., 1978). Singer (1977) interprets this difference as meaning that the corticofugal influence suppresses potentially diplopic images and facilitates visual transmission of images whose objects lie on the horopter. It is particularly interesting for the present study that these physiological influences are found almost exclusively on X cells (Tsumoto et al., 1978). However, the fact that corticofugal synapses comprise approximately 40-45% of the synapses on both X and Y cells (Sherman & Koch, 1986) indicates a much broader influence of cortex over the LGN (see Pettigrew & Dreher, 1987) which includes Y cells. The excitatory input to the geniculate relay cells is probably mediated by a direct connection made via glutaminergic excitatory synapses (Ahlsen, Grant, & Lindstrom, 1982; Fonnum, Storm-Mathison, Divac, 1981).

Inhibitory input is thought to be disynaptic (Tsumoto et al., 1978), arising from excitatory input to intrageniculate interneurons and perhaps perigeniculate cells which in turn form inhibitory synapses on relay cells (Dubin & Cleland, 1977). The rather precise control over the inhibitory input suggested by Schmielau and Singer (1977) and Tsumoto et al. (1978) may mean that intrageniculate interneurons and not perigeniculate cells are involved since the large dendritic spread of the perigeniculate cells (see Sherman & Koch, 1986) is indicative of inhibition of a more global nature (Singer, 1977).

The fact that these interactions occur between the LGN and visual cortex indicates not only that the visual cortex is involved in the binocular visual integrative processes in the LGN but also perhaps binocular-visual/ proprioceptive integration since visual cortex is known to be sensitive to proprioceptive influences (Buisseret & Maffei, 1977; Ashton et al., 1984). The types of integration shown by Schmielau & Singer (1977) and Tsumoto et al., (1978) are difficult to interpret in the context of monocular paralysis since they were demonstrated using paralyzed/anesthetized animals. However, since the distance between the observer and fixation point changes from moment to moment, the corresponding points on the retina (and thus the cells in the laminae of the LGN responding to these points) which must be inhibited or excited to maintain binocular vision without diplopia must change accordingly. To provide this constantly changing modulatory input to the LGN, different corticofugal outputs must be activated according to relative eye position. If this eye position signal originates in the proprioceptors of the extraocular muscles then this role for the integration of binocular visual with binocular proprioceptive information in visual cortex would be very attractive. Since the monocular paralysis effect is the result of the operation of binocular-visual/proprioceptive integration the relationship between the monocular

paralysis effect and the suggested role for the corticofugal input to the LGN seems plausible though the exact cause of the monocular paralysis effect remains unclear.

Summary. In summary, visual cortex, known to be part of a extrathalamic circuit, the functional integrity of which is necessary for the maintenance of the monocular paralysis effect, has been shown to interact with elements of the brainstem reticular formation, through which the cerebellum exerts its own influence in the maintenance of the monocular paralysis effect.

The Role of Anesthesia in the Maintenance of the Monocular Paralysis Effect

The fact that anesthesia and cerebellar lesions have the same effect on the encounter rate for X cells in the monocularly paralyzed cat suggests the possibility that anesthesia produces its effect by temporarily blocking the transmission of cerebellar input to the LGN. Indeed, the cerebellum is sensitive to anesthesia (Fuchs & Kornhuber, 1969). However, there are multiple sites in the brain which are sensitive to anesthesia (cortex [see Richard, Gioanni, Kilsikis & Buser, 1975]; brainstem reticular formation [e.g., Takaori, Nakai, & Sasa, 1975]; and cerebellum [Fuchs & Kornhuber, 1969]) and any one or all of these could contribute to the maintenance of the monocular paralysis effect. Indeed, these sites that are sensitive to anesthesia overlap with sites the lesion of which have been shown to reverse the monocular paralysis effect (visual cortex [Moore et al., 1988]; cerebellum [present study]) or logically may be involved because they may transmit signals from the cerebellum to the LGN (brainstem reticular formation). Consideration of both of these lines of evidence make it impossible to infer the site of action of anesthesia critical for the monocular paralysis effect.

The Monocular Paralysis Effect and Cerebellar Involvement in Eye Movements and Neural Plasticity

It has been shown that cerebellar lesions reverse the monocular paralysis effect thereby increasing the X cell encounter rate, but what does this mean in terms of cerebellar involvement in the monocular paralysis effect? First of all, it must be assumed that over the six days required for the monocular paralysis effect to manifest itself, some physiological change is occurring in the visual system that results in the inhibition of X cells relative to Y cells which characterizes the monocular paralysis effect. This change could be the result of the creation of new circuitry or a modification of existing synapses. Secondly, this physiological change, manifested as the monocular paralysis effect, is the result of binocular-visual/proprioceptive integrative processes (the evidence for this is reviewed in the Introduction) which are at least partly dependent on the cerebellum for their integration and modification. This implies that either: 1) the cerebellum provides no information essential to the integrator but has input to it which, if severed, interrupt, at least for several hours, the integrator's modulation of the X cell encounter rate; 2) the cerebellum is supplying visual and/or proprioceptive information necessary for this integrator of information to function and, as a consequence of the monocular paralysis surgery, to change the X cell encounter rate (i.e., cerebellar output induces creation of new or modification of old synapses); or 3) the cerebellum is the site of the change that is completed within six days post-operative which results in the monocular paralysis effect. The present study cannot distinguish between these three alternatives, but an analysis of the visuo-motor functions of the cerebellum might yield clues about not only cerebellar involvement in the monocular paralysis effect, but the nature and plasticity of binocular-visual/proprioceptive integration and how these elements of the visual system contribute to strabismic amblyopia.

Vergence eye movements. It is possible that the monocular paralysis effect reflects the operation of some mechanism whose purpose it is to properly align the eyes (motor fusion). The role of the cerebellum in the monocular paralysis effect and the cerebellum's important role in eye movements then demands the question: does the cerebellum play a role in vergence eye movements- movements that permit binocular viewing? This seems likely given its importance in other types of eye movements, but little research has been done on this topic. However, there are clinical reports in the literature that demonstrate loss of fusion or vergence eye movements in cases of cerebellar lesions (Lippmann, 1944; Stanworth & Mein, 1971).

There is some experimental support for the idea that the cerebellum is involved in the control of vergence eye movements. Donaldson and Hawthorne (1979) have found that a subpopulation of neurons in the visual vermis (lobules VI and VII) are sensitive to visual disparity. They suggested that the function of these neurons may be to control vergence and perhaps participate in the calculation of visual depth perception and the estimation of the absolute distance of objects from the animal (Donaldson & Hawthorne, 1979). Often it is assumed that visual cortex performs such functions, but recently it has been demonstrated that binocular depth perception in adult cats (as measured using the visual cliff), can be reinstated after visual cortex ablation within eight to ten days post-operative with locomotor experience and concomitant administration of amphetamine during the experience (Feeney & Hovda, 1985). This is an exciting finding in light of the results of the present study which suggests the involvement of the cerebellum in binocular-visual/proprioceptive integration and its plasticity. It is interesting that the recovery of depth perception was dependent on amphetamine, a catecholamine agonist, since numerous studies have implicated catecholamines in the plasticity of the visual

system (Bear & Daniels, 1983; Bear et al., 1983; Bear & Singer, 1986; Gordon et al., 1986; Kasamatsu, 1983; Kasamatsu & Pettigrew, 1976; 1979; Kasamatsu et al., 1979; Pettigrew & Kasamatsu, 1978) and in the manifestation of the monocular paralysis effect (Guido, Salinger, & Schroeder, 1982).

If the cerebellum is involved in the control of vergence eye movements and receives information about retinal disparity then it might also be involved with the suppression of X cells whose receptive fields lie off of the horopter (a model for binocular fusion). Since the monocular paralysis effect is a suppression of X cells with central receptive fields in both the paralyzed and nonparalyzed eyes, it could be that this effect is caused by mechanisms which facilitate binocular fusion. In summary, it is possible that the lesion of the cerebellum could destroy the function of a system involved with binocular fusion, a system which may be modified by monocular paralysis.

Saccadic eye movements. It is possible that rather than binocular fusion being central to the monocular paralysis effect, saccadic eye movements, which are prevented in one eye of the monocularly paralyzed animal, are more central to the monocular paralysis effect. One report from the literature that makes this an attractive possibility involves the recovery of saccadic eye movements in adult patients with unilateral abducens nerve palsy (a condition with similarities to adult monocular paralysis). In these patients, the oculomotor system apparently can recover from a peripheral injury by changing the phasic component (to increase the size of the saccade) and the tonic component (to prevent post-saccadic drift) (Kommerell, Olivier, & Theopold, 1976). Interestingly, these recoveries can be made after patching the normal eye within about three days (Kommerrell et al., 1976), similar to the period of time it takes for the monocular paralysis effect to manifest itself (6 days; unpublished observations).

The recovery of saccades which is dependent on experience in the eye in which the innervation of the extraocular muscle has been compromised may be considered an example of adult neural plasticity. Of special relevance to the present study, however, is that this plasticity can be completely eliminated by destroying the visual vermis of the cerebellum (Optican & Robinson, 1980). These results are consistent with the hypothesized function of this area of the cerebellum, mentioned previously, which is to modify and increase the accuracy of saccades, but are they related to the findings of the present study which show cerebellar influence on the processing of visual information in the geniculo-striate system?

It might be speculated that the monocular paralysis effect is related to a mechanism involved with saccadic suppression. The parallel between the present study (the monocular paralysis effect reversed by cerebellar lesion) and the finding that the removal of part of the cerebellum prevents changes which normally would occur as a result of the reduced motility of one eye is obvious, but the change that we observe as a result of monocular paralysis is a change in the relative encounter rates of X and Y cells, <u>not</u> a change in motor behavior (which would be impossible since the eye is completely paralyzed). The clinical report (Kommerell et al., 1976) mentions nothing about visual suppression in the paretic or normal eye that might be related to the monocular paralysis effect so the relationship between this adaptation of saccades and monocular paralysis is not clear. However, if the increased visual threshold during saccades is due to the suppression of X cells, it may be speculated that the monocular paralysis effect is produced by adaptive changes in the neural mechanism responsible for the control of saccade gain as well as saccadic suppression. That is, it is possible that as the gain of the saccadic mechanism is increased (in an attempt to create normal saccades despite the failed

musculature) the saccadic suppression mechanism is increased or constantly initiated (since no saccade is forthcoming) resulting in the suppression of X cells. The increased visual thresholds during saccadic eye movements (saccadic suppression) may, in fact, be due to X cell suppression, but the source of suppression has not been localized and may not be an active suppression at all, but merely the result of retinal smear (Matin, 1974; Mitrani, Mateef, & Yakimoff, 1970) or visual masking (Lefton, 1972; Matin, Clymer, & Matin, 1972; Weisstein, 1972).

Cerebellar Involvement in Neural Plasticity

Monocular paralysis has previously been suggested to involve neural plasticity since the change in X cell encounter rate does not occur immediately, but requires six days to manifest itself (Brown & Salinger, 1975; unpublished observations). Since the cerebellar lesions reversed the monocular paralysis effect it could be suggested that the cerebellum is the site of this neural plasticity. Indeed, the adaptability (and, thus, plasticity) of the vestibulo-ocular reflex (Ito, Jastreboff, Miyashita, 1982; Robinson 1976) and saccades (Kommerall et al., 1976; Optican & Robinson, 1980) has been shown to rely on the functional integrity of structures within the cerebellum. However, it must be pointed out that substantial evidence exists that visual cortex is also involved with the plasticity of the developing visual system (Hubel & Wiesel, 1970; Wiesel & Hubel, 1963; 1965). Since lesions of visual cortex also reverse the monocular paralysis effect (Moore et al., 1988), it is not possible to say whether neural plasticity mechanisms in visual cortex, cerebellum or both are involved in the monocular paralysis effect.

Even though the site of changes that occur as a result of monocular paralysis can not be localized to one particular structure the present study and other investigations of extrathalamic structures in involved in the monocular

paralysis effect (Moore et al., 1988) give some direction to future studies that may investigate the site of this form of plasticity. It has been shown that changes in developing visual cortex that occur as a result of alterations in visual stimulation depend on the normal presence of catecholamines (Bear & Daniels, 1983; Bear et al., 1983; Bear & Singer, 1986; Gordon et al., 1986; Kasamatsu, 1983; Kasamatsu & Pettigrew, 1976; 1979; Kasamatsu et al., 1979; Pettigrew & Kasamatsu, 1978). Indeed, intraventricular administration of 6-hydroxydopamine (which destroys catecholaminergic cells) during the period following monocular paralysis seems to prevent changes in the relative encounter rates for X and Y cells that have otherwise been shown to occur in this preparation (Guido et al., 1982). More discrete applications of 6-hydroxydopamine in visual cortex, the cerebellum, and perhaps LGN of different animals after monocular paralysis might reveal which one or combination of these structures is the sight of plastic changes that occur as a result of monocular paralysis. Insofar as the monocular paralysis effect is a model for processes that occur in strabismic amblyopia such a series of experiments may help to isolate sites critical for amblyopia.

Cerebellar involvement in Strabismic Amblyopia

To date there are no theories of strabismic amblyopia that integrate ideas about the source of errors in oculomotor control which are likely to be at the heart of strabismus with defects in visual sensory processing which constitute amblyopia. Instead, most current models of strabismic amblyopia focus exclusively on the visual sensory processing abnormalities in the geniculo-striate system (von Noorden, 1985; Boothe et al., 1985). In these theories the geniculo-striate abnormalities could either be caused by the strabismus or give rise to it. There are several potential causes of strabismus ranging from anatomic or mechanical interferences with eye movement because of congenital

malformation or trauma, to functional or innervational abnormalities (Flax, 1983). Also, the accommodative effort necessary to compensate for an uncorrected hyperopia may result in a loss of eye alignment because it induces so great an accommodative convergence response that the fusional vergence capability of the patient is overwhelmed (Flax, 1983). In each of these cases the subsequent amblyopia is thought to arise secondarily because of binocular rivalry and suppression of one image (e.g., Sireteanu & Fronius, 1981; Smith et al., 1985) or perhaps because of chronic defocusing of the deviating eye which could result in an arrest in the development of acuity (Ikeda et al., 1977; Ikeda & Tremain, 1979; Ikeda & Wright, 1974; 1976; Jacobson & Ikeda, 1979). It is also logically possible that amblyopia arising from some other condition (e.g., visual deprivation, anisometropia) prevents fusional lock and therefore results in strabismus.

If one considers that the monocular paralysis effect is a model for at least some aspects of strabismic amblyopia, the facts that: 1) the cerebellum is part of an extrathalamic circuit supporting the monocular paralysis effect and 2) the cerebellum is highly involved in the production of eye movements, suggest the conclusion that, perhaps, that the cerebellum is involved with strabismic amblyopia. The fact that cerebellar lesions reversed the X cell suppression of the monocular paralysis effect (a possible model for the suppression arising from strabismus whose chronic presence during development may result in amblyopia) suggests that abnormalities in the oculomotor plant (perhaps the cerebellum) not only produces amblyopia by misaligning the eyes but directly influence visual transmission through the geniculo-striate system in which the subsequent amblyopia is manifested. This modulation of the visual transmission through the geniculo-striate system by the cerebellum may be accomplished by the connections of the cerebellum to the brainstem reticular formation whose

input to the LGN has been shown to exert a powerful influence over geniculate processing of visual information. It seems reasonable to propose then that the cerebellum, with its sensitivity to visual and extraocular muscle proprioceptive information, its control over eye movements, and its obvious influence (revealed here) over the geniculo-striate system, may be of central importance to the etiology of strabismic amblyopia.

Suggestions for Further Research

One line of inquiry, demanded by the finding that the cerebellum reversed the monocular paralysis effect, is that of determining the pathway by which this cerebellar control over geniculate processing occurs. As noted in previous sections, the cerebellum has no direct connections to the LGN. Therefore it was hypothesized that the cerebellum controlled geniculate processing via the brainstem reticular formation, which receives input from the cerebellum and in turn richly innervates the LGN. Knowledge of the neurotransmitters involved would be helpful in specifying the pathway since the three main inputs from the brainstem to the LGN used different neurotransmitters. Therefore pharmacological blockade of certain synapses in the perigeniculate-LGN complex after monocular paralysis could reveal the critical neurotransmitter(s) that contribute to the monocular paralysis effect by inducing a reversal of the effect. One experiment of this kind was offered (in a previous section) as a test of the hypothesis that cholinergic control of perigeniculate cells may contribute to the monocular paralysis effect.

Certainly one of the key aspects of the present study that could be improved upon is that of localizing the particular area of the cerebellum the lesion of which reverses the monocular paralysis effect. This is a challenge because the cerebellum is so large and the X cell encounter rate is so time consuming to determine that assessing the effect of many lesions would be

correspondingly tedious. However, it may be possible to observe gross changes in the X cell encounter rate in evoked potentials time-locked to optic nerve stimulation by comparing the amplitudes of peaks corresponding to the conduction times for X and Y cells. This relatively quick way of assessing the X cell encounter rate would allow for multiple lesion-record cycles that would enable one to pinpoint the area of the cerebellum involved in the monocular paralysis effect. This would be a valuable finding by itself because the knowledge already gained about a particular area of the cerebellum may yield significant clues about the nature of the monocular paralysis effect. Determining the effects of a lesion of this specific area of the cerebellum in the developing organism may lead to better animal models of strabismic amblyopia.

Once the critical area in the cerebellum for the maintenance of the monocular paralysis effect or has been located many avenues of investigation could be explored. For example, the response of LGN neurons to stimulation of this particular area of the cerebellum and perhaps interactions with visual stimulation would be very interesting. A more detailed knowledge of pathways to the LGN from this area of the cerebellum, obtained through HRP studies of the anatomical connections, would certainly yield more clues about the properties of the circuitry on the monocular paralysis effect. In addition, indications in the literature of this particular area's function and connections to other structures might reveal new insights into the circuitry of the monocular paralysis effect and, perhaps, the etiology of strabismic amblyopia. In this regard, lesions of this or perhaps other areas of the cerebellum may serve to produce a strabismus-like condition in experimental animals which may provide researchers with a more appropriate model of strabismic amblyopia.

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APPENDIX A

INDIVIDUAL DATA

Table A-1. Percentages of X, Y, and unclassified (UC) cells, encountered in each lamina of each animal under Pre-op. sedated, Pre-op. anesthetized, and Post-op. cerebellar (Cb) lesion conditions.

		Pre-lesion sedated		Pre-lesion anes.		Post-Cb lesion	
		%	N	%	N	%	N
Animal #1133							
Lamina A							
	X	28.57	2	-	-	50.00	4
	Y	71.43	5	-	-	50.00	4
	UC	0	0	-	-	0	0
Lamina A1							
	X	25.00	3	-	-	62.50	5
	Y	75.00	9	-	-	37.50	3
Animal #1184							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-Cb lesion	
		%	N	%	N	%	N
	X	20.00	1	50.00	2	85.71	6
	Y	60.00	3	50.00	2	14.29	1
	UC	20.00	1	0	0	0	0
Lamina A1							
	X	15.38	2	66.67	2	88.89	8
	Y	84.62	11	33.33	1	11.11	1
Animal #1197							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-Cb lesion	
		%	N	%	N	%	N
	X	40.00	8	62.50	5	54.55	6
	Y	55.00	11	37.50	3	45.45	5
	UC	5.00	1	0	0	0	0
Lamina A1							
	X	23.08	3	100.00	4	66.67	6
	Y	76.92	10	0	0	33.33	3

Table A-1. (cont.)

Animal #1198							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-Cb lesion	
		%	N	%	N	%	N
	X	50.00	10	100.00	3	80.00	8
	Y	50.00	10	0	0	20.00	2
	UC	0	0	0	0	0	0
Lamina A1							
	X	28.57	8	75.00	6	66.67	6
	Y	71.43	20	25.00	2	33.33	3

Table A-2. Percentages of X, Y, and unclassified (UC) cells, encountered in each lamina of each animal under Pre-lesion sedated, Pre-lesion anesthetized, and Post-collicular (SC) lesion conditions.

Animal #1309							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-SC lesion	
		%	N	%	N	%	N
	X	57.14	4	70.00	7	-	-
	Y	42.86	3	30.00	3	-	-
	UC	0	0	0	0	-	-
Lamina A1							
	X	16.67	1	62.50	10	16.67	1
	Y	83.33	5	37.50	6	83.33	5
Animal #1312							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-SC lesion	
		%	N	%	N	%	N
	X	23.08	3	61.54	8	30.00	3
	Y	76.92	10	30.77	4	60.00	6
	UC	0	0	7.69	1	10.00	1
Lamina A1							
	X	14.29	1	70.00	7	0	0
	Y	85.71	6	30.00	3	100.00	0
Animal #1316							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-SC lesion	
		%	N	%	N	%	N
	X	42.86	6	77.78	7	28.57	2
	Y	42.86	6	22.22	2	71.43	5
	UC	14.29	2	0	0	0	0
Lamina A1							
	X	25.00	2	83.33	5	3.636	4
	Y	75.00	6	16.67	1	63.64	7
Animal #1317							
Lamina A		Pre-lesion sedated		Pre-lesion anes.		Post-SC lesion	
		%	N	%	N	%	N
	X	16.67	1	77.78	7	10.00	1
	Y	66.67	4	11.11	1	90.00	9
	UC	16.67	1	11.11	1	0	0
Lamina A1							
	X	16.67	1	50.00	2	14.29	1
	Y	83.33	5	50.00	2	85.71	6

APPENDIX B

STATISTICAL SUMMARY TABLES

Table B-1. Analysis of variance of the frequency of X cells for subjects in the cerebellar lesion group.

Source	df	MS	F	PR < F
Model	5	.2020	8.17	.0005
Error	16	.0247		
Corrected total	21			
Condition	2	.4831	19.54	.0001
Lamina	1	.0001	00.01	.9341
Cond. x Lam.	2	.0219	00.89	.4315
Error	16	.0625		
Contrasts				
Sed vs. Anes (A)	1	.2245	9.08	.0082
Sed vs. Anes (A1)	1	.5677	22.96	.0002
Sed vs. Cb lesion (A)	1	.2167	8.77	.0092
Sed vs. Cb lesion (A1)	1	.4641	18.77	.0005

Table B-2. Analysis of variance of the frequency of X cells for subjects in the collicular lesion group.

Source	df	MS	F	PR < F
Model	5	.2406	14.19	.0001
Error	17	.0169		
Corrected Total	22	1.4914		
Condition	2	.5477	32.30	.0001
Lamina	1	.0613	3.62	.0743
Cond. x Lam.	2	.0131	0.77	.4779
Error	17	.0169		
Contrasts				
Sed vs. Anes (A)	1	.2457	14.49	.0014
Sed vs. Anes (A1)	1	.4911	28.96	.0001
Sed vs. SC lesion (A)	1	.0329	1.94	.1812
Sed vs. SC lesion (A1)	1	.0000	0.00	.9935

APPENDIX C

CEREBELLAR LESIONS

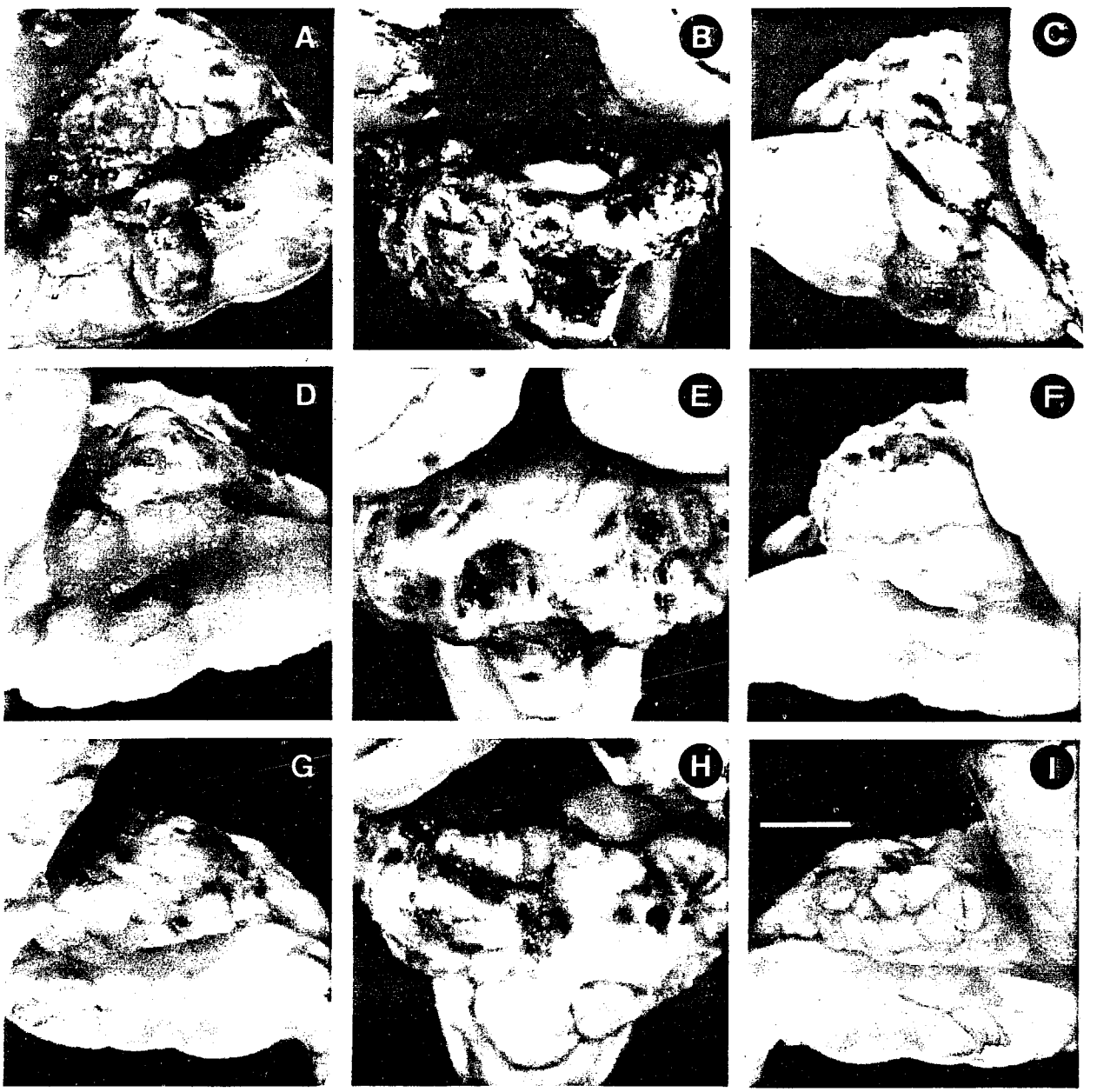

Figure C-1. Left side, right side, and dorsal veiws (shown left to right) of cerebellar lesions #1184 (A-C), #1197 (D-F), and #1198 (G-I). Scale bar represents 5 mm. See Figure 3 in the main text for comparison to the cerebellar area of a normal brain shown also with the cerebellum completely dissected away to expose the pons.

APPENDIX D

COLLICULAR LESION RECONSTRUCTIONS

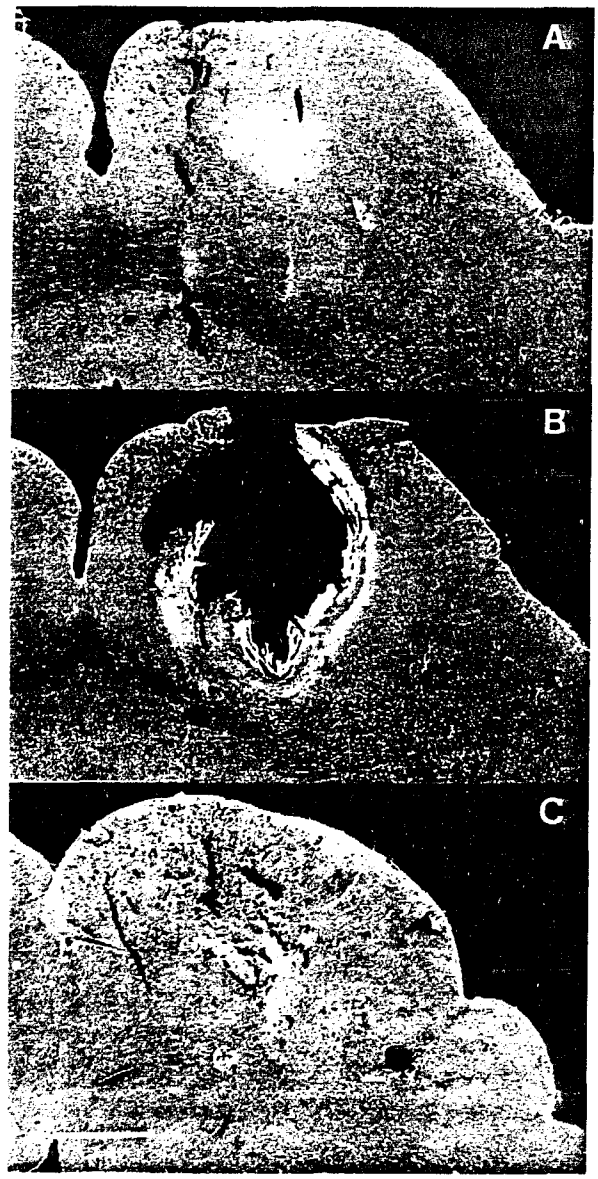

Figure D-1. Three views of collicular lesion #1309 are shown. A photographic emulsion was exposed to the enlarged image of unstained slides (20 μm thick, 1.5 mm apart) representing the rostral extreme (A), geometric center (B), and caudal extreme (C) of the lesion. The lesion was created by .32 Amp-seconds of current passed through a monopolar electrode (teflon-coated medwire, 0.010 in. diameter, insulated except for the tip,). Scale bar represents 1 mm.

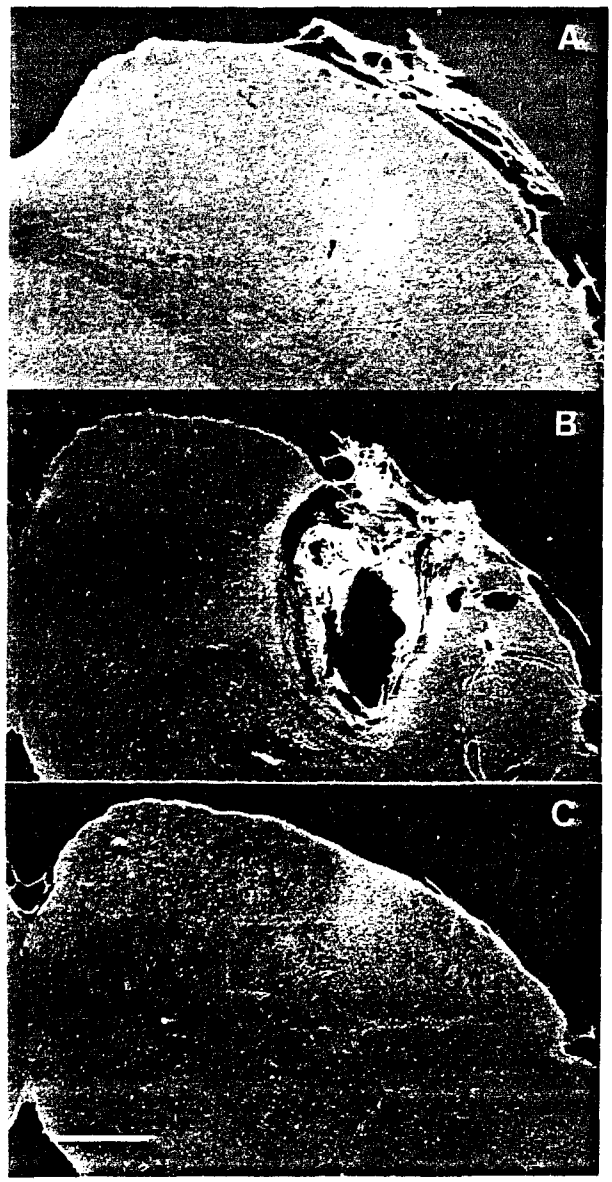

Figure D-2. Three views of collicular lesion #1312 are shown. A photographic emulsion was exposed to the enlarged image of unstained slides (20 μm thick, 1.0 mm apart) representing the rostral extreme (A), geometric center (B), and caudal extreme (C) of the lesion. The lesion was created by .49 Amp-seconds of current passed through a monopolar electrode (teflon-coated medwire, 0.010 in. diameter, insulated except for the tip,). Scale bar represents 1 mm.

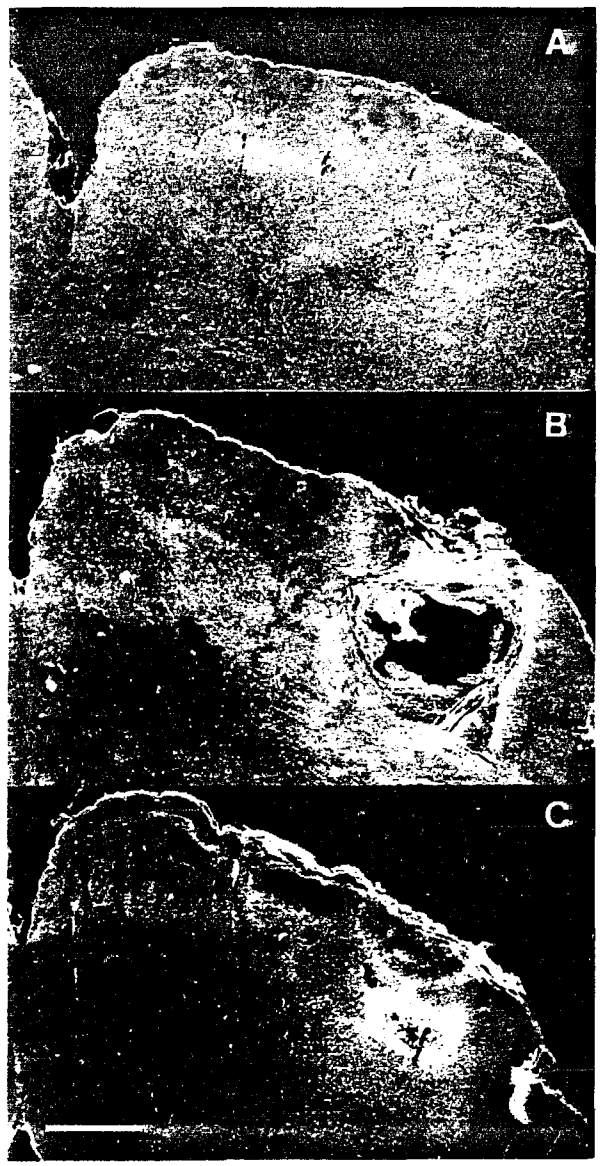

Figure D-3. Three views of collicular lesion #1317 are shown. A photographic emulsion was exposed to the enlarged image of unstained slides (20 μm thick, 1.3 mm apart) representing the rostral extreme (A), geometric center (B), and caudal extreme (C) of the lesion. The lesion was created by .38 Amp-seconds of current passed through a monopolar electrode (teflon-coated medwire, 0.010 in. diameter, insulated except for the tip,). Scale bar represents 1 mm.

APPENDIX E

COLLICULAR LESIONS: RETINOTOPIC PLACEMENT

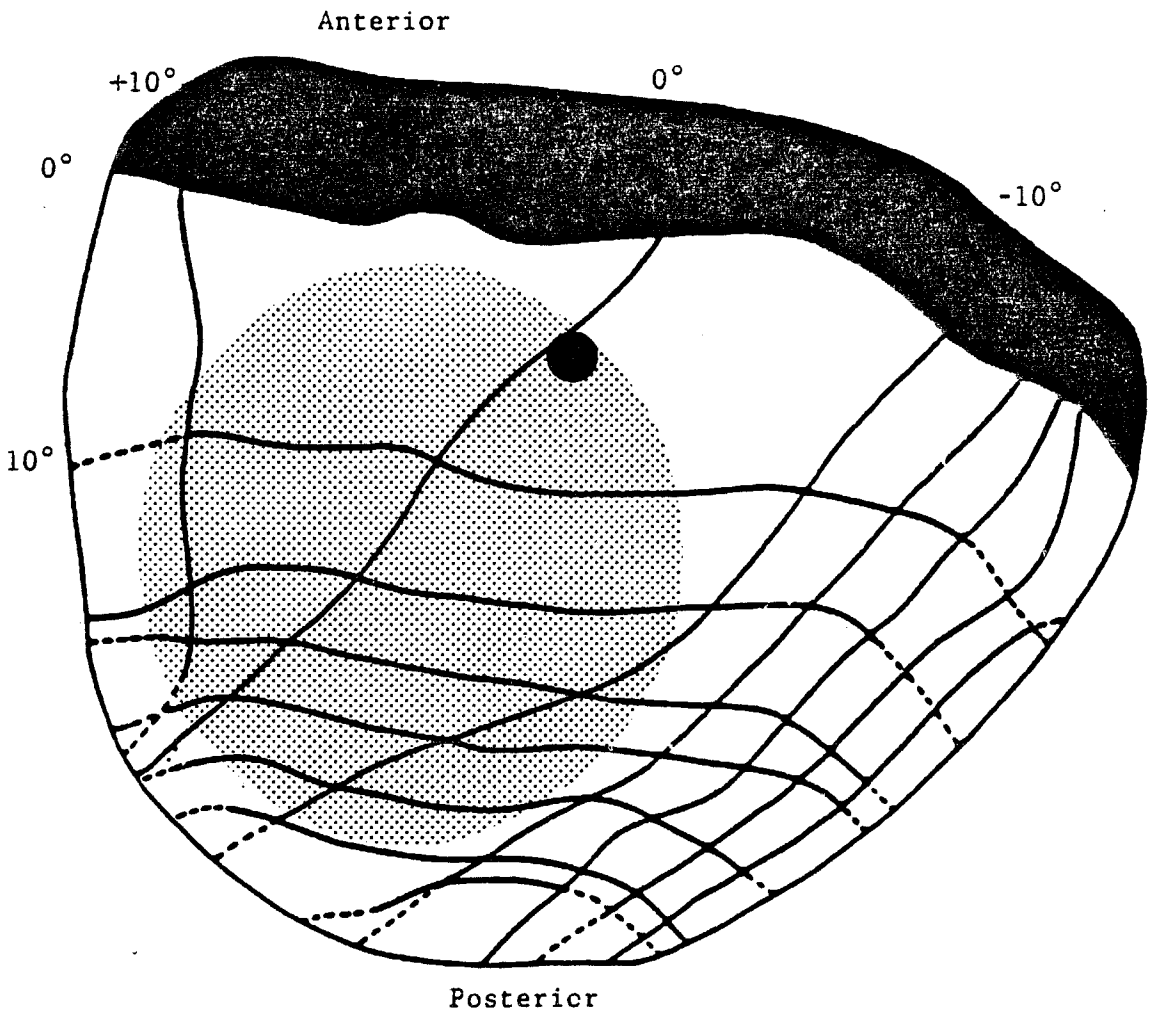

Figure E-1. A retinotopic map of the superior colliculus is shown with a representation of collicular lesion #1309 (stipled area) and the position in visual space of the retinotopically matched LGN recording penetration (dot). Horizontal lines represent the vertical meridian and isoazimuth lines. The more nearly vertical lines represent the horizontal meridian and isoelevation lines. The collicular representation of ipsilateral visual space is shown in black. Modified from Feldon, Feldon, and Kruger (1970).

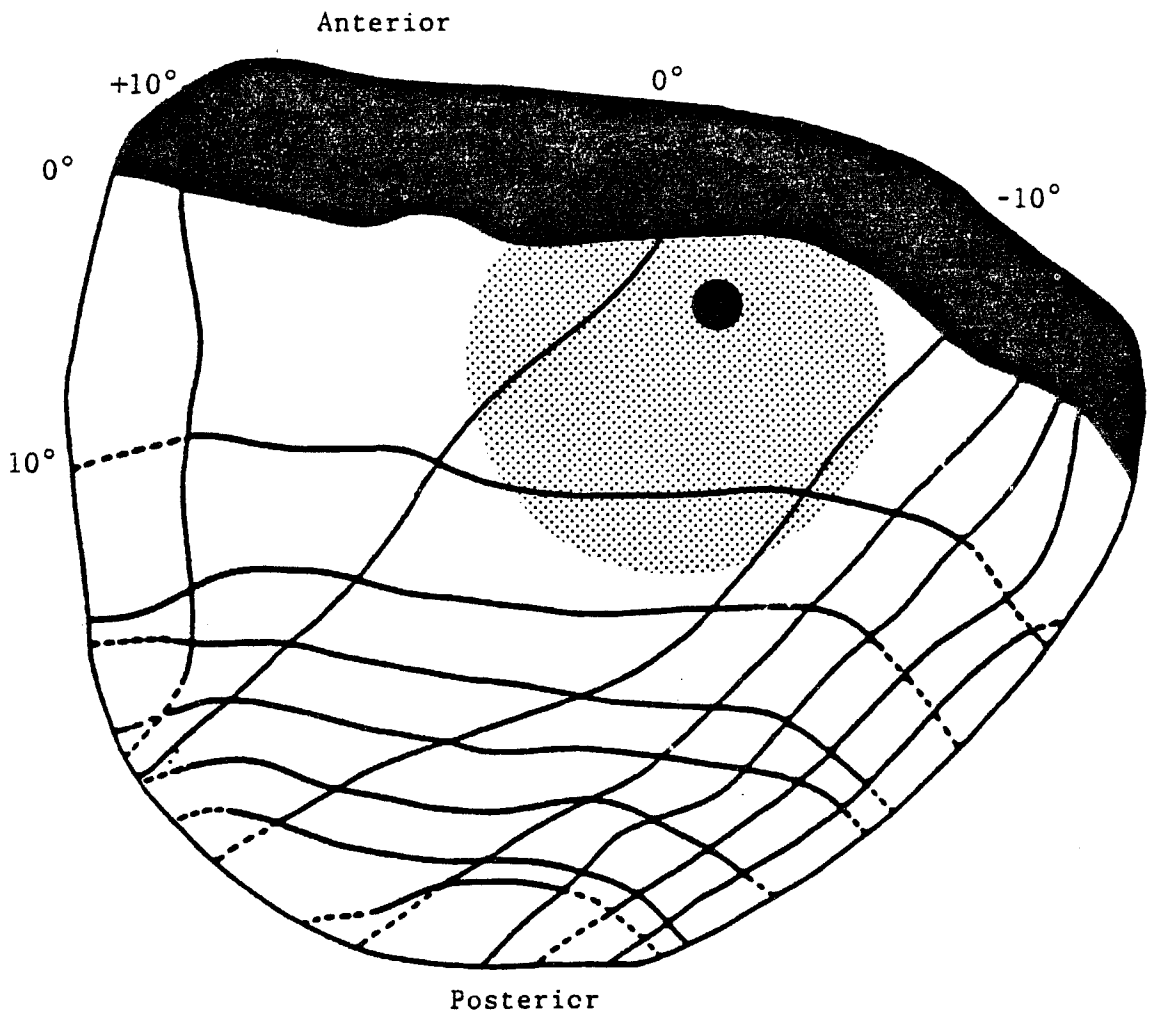

Figure E-2. A retinotopic map of the superior colliculus is shown with a representation of collicular lesion #1312. Otherwise the same as Figure E-1.

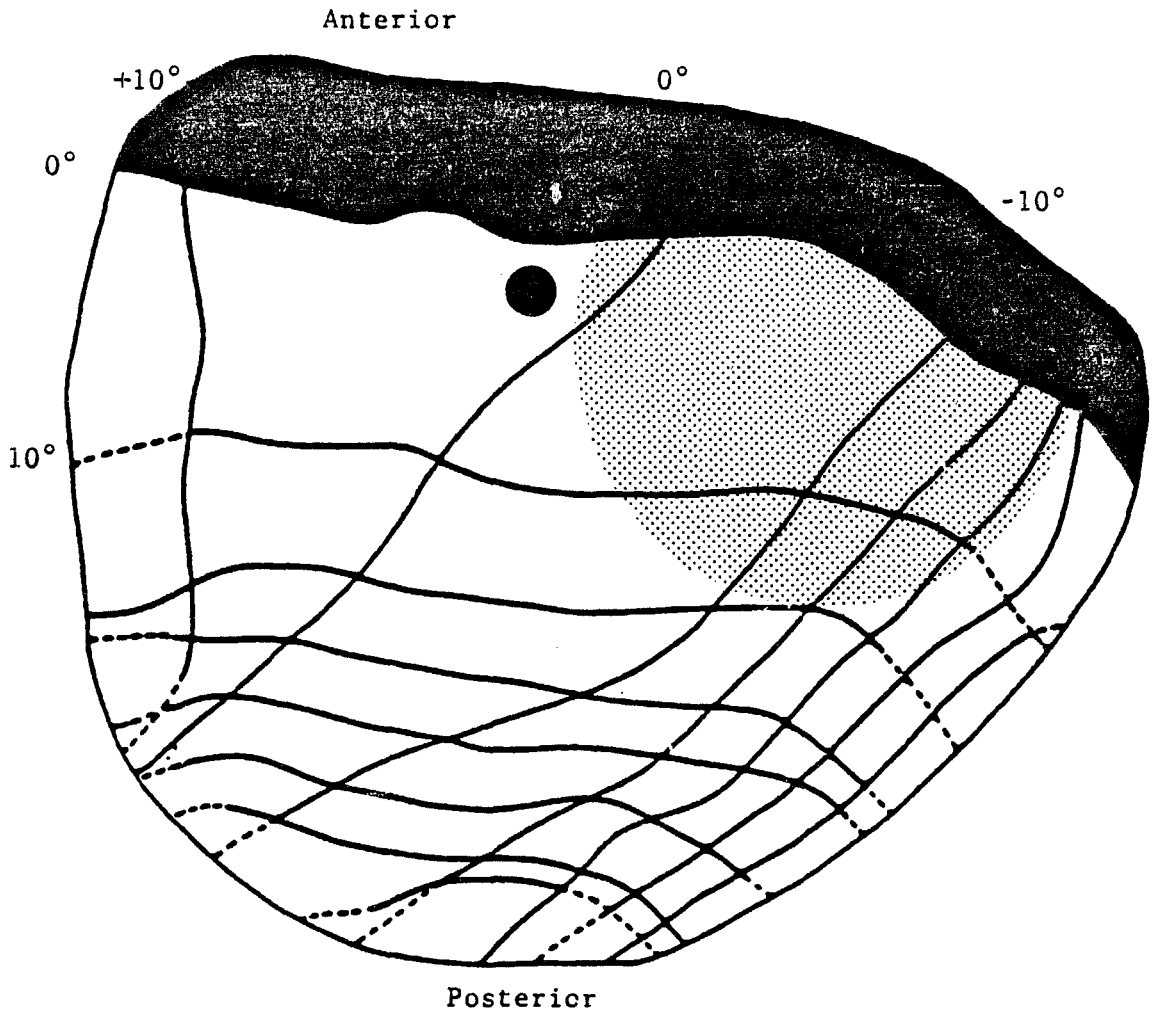

Figure E-3. A retinotopic map of the superior colliculus is shown with a representation of collicular lesion #1317. Otherwise the same as Figure E-1. Note: Since both the lesion and the retinotopic map were created using physiological criteria (but in different animals) variability between animals in the representation of visual space in the superior colliculus may explain the apparent discrepancy in the above figure.