Schroeder, Charles Emil

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

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ANESTHETIC EFFECTS UPON EXCITABILITY AND RELATIVE ENCOUNTER RATES FOR X- AND Y-CELLS IN THE LATERAL GENICULATE NUCLEUS (LGN) OF ADULT CATS

by

Charles E. Schroeder

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Disruptions in binocular stimulation induced by two or more weeks of monocular paralysis (ChMP), reduce the encounter rates for X- relative to Y-type LGN cells (a reduction in the X/Y ratio) during semichronic recordings from adult cats. Less than four days of monocular paralysis (AcMP) has no impact upon the X/Y ratio. The processes underlying ChMP's impact upon the X/Y ratio are not passive or degenerative, and are therefore active processes such as 1) excitability changes in X-cells, in Y-cells, or in both cell types; or 2) change in the functional characteristics of X-cells such that they are systematically reclassified as Y-cells. These alternatives were explored using standard extracellular unit recording procedures, including classification of cells as X- or Y-type with a common battery of receptive field and physiological measures. Preliminary experiments indicated that nitrous oxide anesthesia reverses the impact of ChMP, rendering the X/Y ratio of ChMP equivalent to that of AcMP (which is unaffected by anesthesia), and that this effect is so robust that it is evident in single electrode penetrations. Therefore, the above alternatives could be evaluated indirectly, by using ChMP/anesthetized as an analogue for AcMP. While maintaining contact with each cell, we shifted the animal between anesthetized and unanesthetized states, measuring the cell's receptive field and/or electrophysiological properties in each state. Application of this procedure to a series of single units revealed that 1) in AcMP, anesthesia has no systematic impact upon any unit property (ruling out any effects of anesthesia per se); and 2) in ChMP, anesthesia has no effect on the receptive field

classification, or upon the components of retinogeniculate conduction time (ruling out possible change in the functional identity of X-cells), but anesthesia does produce a systematic increase in the excitability of X-cells and a decrease in the excitability of Y-cells. This reciprocal change in the excitability of X- and Y-cells parallels, and thus may underlie the anesthesia-related increase in the X/Y ratio of ChMP. By implication, reduction in the X/Y ratio after ChMP may result from the inverse process: decrease in X-excitability and increase in Y-excitability. Such a modulation of excitability may reflect aspects of the physiology underlying normal binocular integration.

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CHAPTER I

INTRODUCTION

Neural plasticity refers to the brain's ability to alter an established pattern of responding when cued by a significant change in the pattern of input. Neural plasticity presumably underlies an organism's ability to demonstrate behavioral flexibility and thus relates to a variety of phenomena ranging from compensations for injury or alteration of input, to accommodation to changes that accompany learning, development, and aging. Neural plasticity is traditionally investigated in terms of developmental processes (e.g., see Stewart, Cotman & Lynch, 1973; Lynch, Stanfield & Cotman, 1973; Lund, 1978; Greenough & Green, 1981); however, more recently, it has been observed in the adult as well (Brown & Salinger, 1975; Buchtel, Berlucci & Mascetti, 1975; Fiorentini & Maffei, 1974; Maffei & Fiorentini, 1976; Hoffmann & Cynader, 1977; Salinger, Schwartz & Wilkerson, 1977a; 1977b; Wilkerson, Salinger & MacAvoy, 1977; Kasamatsu, 1979, 1982; Kasamatsu, Pettigrew & Ary, 1979; Salinger, Garraghty & Schwartz, 1980; Salinger, Garraghty, MacAvoy & Hooker, 1980; Kasamatsu, Itakura & Johnsson, 1981; Garraghty, Salinger, MacAvoy, Schroeder, & Guido, 1982).

One of the earliest manifestations of <u>adult</u> neural plasticity was observed in the visual system, following monocular paralysis (Brown & Salinger, 1975). Monocular paralysis is an experimental preparation

that entails surgical immobilization of one eye by transection of cranial nerves III, IV, and VI. This preparation was initially developed as an alternative to systemic paralysis (generally viewed as the "normal preparation") for the purpose of stabilizing the position of the eye, to permit analysis of the receptive field properties of single neurons in the visual system of the cat (e.g. Schiller & Koerner, 1971). Monocular paralysis, in the acute phase (i.e., less than 4 days duration), performs well in this regard, permitting examination of single unit activity in the LGN and yielding LGN X- and Y-cell encounter rates which are consistent with those obtained from systemically paralyzed cats (Salinger et al., 1977a; Garraghty et al., 1982). In the early experiments concerning monocular paralysis, however, an effect that directly relates to adult neural plasticity was observed: When the duration of monocular paralysis exceeded 13 days, there was a significant reduction in the electrophysiological encounter rate for LGN X- relative to Y-type cells, or in other terms, a reduction in the X/Y ratio (Brown & Salinger, 1975; Salinger et al., 1977a).

Critical Stimulus Dimensions of Monocular Paralysis

Monocular paralysis represents a complex sensory-motor modification, with a variety of stimulus dimensions affected. A series of experiments examined the stimulus features of monocular paralysis, which are critical for promoting the reduction in the X/Y ratio. These experiments indicated that the cues which initiate X/Y ratio reduction are binocular in character, since they stem from misalignment of one eye relative to the other (Salinger, Garraghty, & Schwartz, 1980). Further, these cues are both retinally mediated, e.g., abnormal retinal

disparities, and extraretinally mediated, e.g., proprioceptive asymmetry (Salinger, Garraghty, & Schwartz, 1980). Finally, the extent of the reduction in the X/Y ratio was shown to depend upon the symmetry of ocular paralysis (Wilkerson, Salinger, & MacAvoy, 1977; Schroeder & Salinger, 1978), upon the visuotopic area of the LGN investigated (Garraghty et al., 1982), and upon the depth of anesthesia during recording (Garraghty et al., 1982).

The Active Nature of the Mechanism Triggered by Monocular Paralysis

Although the stimulus dimensions of monocular paralysis that are critical for its effect upon the LGN X/Y ratio have been outlined in considerable detail (Salinger et al., 1977b; Wilkerson et al., 1977; Schroeder & Salinger, 1978; Salinger, Garraghty, & Schwartz, 1980; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Garraghty et al., 1982), characterization of the actual brain mechanisms responsible for reducing the X/Y ratio in response to monocular paralysis is by no means complete. With regard to the nature of this mechanism, however, three facets of the research to date suggest that the reduction in the X/Y ratio after monocular paralysis is a functional response of the brain to alteration of input rather than a degenerative or atrophic response to injury. These facets are 1) the capacity of additional sensory modifications, either concurrent with, or subsequent to those induced by monocular paralysis, to reduce or even reverse the physiological impact of monocular paralysis; 2) the fact that a prior pharmacological treatment, targeting the brain's catecholamine systems, prevents monocular paralysis from impacting upon the LGN X/Y ratio; 3) the

observation that the ability to observe an X/Y ratio reduction after monocular paralysis is extremely sensitive to the subject's level of anesthesia during recording.

First, the pattern of sensory modification induced by binocular lid suture, concurrent with monocular paralysis, partially protects the LGN from the physiological impact of monocular paralysis (Salinger, Garraghty, & Schwartz, 1980). Similarly, if a chronic monocular paralysis effect is induced, subsequent paralysis of the second eye, termed sequential paralysis, partially but immediately decreases the amount of reduction in the X/Y ratio (Schroeder & Salinger 1978). The relative encounter rates for X- and Y-cells after sequential paralysis are quite similar to those resulting from paralysis of both eyes induced concurrently, or binocular paralysis (Wilkerson et al, 1977; Schroeder & Salinger, 1978). Neither the results of lid suture, concurrent with paralysis, nor those from binocular paralysis (either sequential or concurrent) would be predicted by an hypothesis of a passive or degenerative process. In either case, the overall insult to the visual system is greater than that caused by monocular paralysis alone, yet the impact on the X/Y ratio is actually less than after chronic monocular paralysis. It would seem, therefore, that an hypothesis of an active mechanism could more easily account for these results.

Secondly, pharmacological treatment aimed at destruction of the brain's catecholamine systems apparently protects the X-cell population from the effects of monocular paralysis (Guido, Salinger, & Schroeder, 1982). This again supports an active over a passive process, since the most likely interpretation of this result is that the neurotoxin used by

Guido et al. (1982), 6-hydroxydopamine (6OHDA), disabled a neurochemically distinct system that was active in suppressing LGN X-cells (thus reducing the X/Y ratio) in response to monocular paralysis.

A final and most compelling support for the hypothesis of an active mechanism stems from the observation that X/Y ratio reduction after monocular paralysis can be immediately reversed by the induction of deep anesthesia with sodium pentobarbital (Garraghty et al., 1982). The fact that the reduction in the X/Y ratio, stemming from chronic monocular paralysis, can be reversed simply by manipulating the animal's level of anesthesia, presents a strong case for the involvement of an active physiological mechanism in this effect, since a degenerative response would not be expected to show this degree of lability.

Interpretation of the Reduction in the X/Y Ratio after Monocular Paralysis

One approach to the identification of the actual brain mechanism underlying the reduction in the LGN X/Y ratio after monocular paralysis is a characterization of the processes that give rise to this change. The term "process" is used here to refer to change in the functional characteristics of LGN units, as distinct from (but not necessarily independent of) change in the nature or activity of neural circuits outside of the LGN. At the present time at least five alternative processes in LGN units could underlie a reduction in the X/Y ratio: 1) suppression of X-cell activity (or X-suppression); 2) facilitation of Y-cell activity (or Y-facilitation); 3) some combination of X-cell suppression and Y-cell facilitation (or combined X-suppression and

Y-facilitation); 4) a distortion in certain X-cell functional properties, such that after chronic monocular paralysis, X-cells, in some respects, functionally resemble Y-cells (or X-response distortion); and 5) unmasking of ordinarily silent Y-type afferents to LGN X-cells, such that X-cells become completely Y-like, in ordinary functional terms (or Y-afferent unmasking). Further, the reports concerning the reduction in the X/Y ratio after chronic monocular paralysis and those concerning the stimulus dimensions of monocular paralysis (see above) are based upon electrophysiological sampling procedures which, by themselves, cannot provide a definitive test of these hypotheses. That is, the sampling procedures used to date (e.g., Brown & Salinger, 1975; Salinger et al., 1977; Garraghty et al., 1982) have revealed a decrease in the LGN X/Y ratio after chronic paralysis but could not distinguish between a reduction in the encounter rate for X-cells and a gain in the encounter rate for Y-cells or some combination of these (hypotheses 1, 2 and, 3). Garraghty et al. (1982) sought to assess hypotheses 1, 2, and 3 more directly, using a measure of sampling density. However, this measure could allow only tentative conclusions, since it was contaminated by extraneous factors, e.g., degree of tissue stability. The hypothesis of X-response distortion was addressed more successfully by Garraghty et al. (1982), yet still not conclusively, since the sampling methods may have obscured subtle effects due to X-response distortion. Finally, hypothesis 5 (Y-afferent unmasking) has simply not been directly assessed. Therefore, because earlier research has not directly addressed all of these hypotheses, and since such attempts, when they have occurred, have yielded limited conclusions, the

information that bears on these hypotheses is derived more often through inference from other studies of LGN physiology than from those studies which were directly concerned with the effects of monocular paralysis.

Principal Evidence Concerning these Hypotheses

1) X-suppression: At the outset, the X-suppression hypothesis would seem to be more likely than the others, as a basis for the chronic monocular paralysis effect, since a) the effects of chronic monocular paralysis stem from disruptions in binocular retinal and extraretinal stimuli, such as distortions in either retinal disparity or the symmetry of ocular proprioception (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980); and b) relative to Y-cells, X-cells appear more sensitive to the impact of both binocular retinal mechanisms (Suzuki & Takahashi, 1970; Fukada & Stone, 1976; Rodiek & Dreher, 1979), and binocular nonretinal mechanisms such as those associated with the control of conjugate eye movements (e.g., see Tsumoto & Suzuki, 1976).

2) Y-facilitation: There is also reason to suggest that Y-cells, like X-cells, may be influenced by retinal and extraretinal binocular stimuli (albeit possibly to a lesser extent than X-cells), but in an opposing, or facilitative direction (e.g., see Fukada & Stone, 1976; Garraghty et al., 1982). For example, in Garraghty et al. (1982), a measure of sampling density suggested that the average number of cells encountered per electrode penetration (or cells per pass) did not differ between acute and chronic monocularly paralyzed subjects. This, in conjunction with a relative increase in the encounter rate for Y-cells (chronic relative to acute), could be interpreted to mean that monocular paralysis causes an increase in the activity of LGN Y-cells, which

balances the hypothesized reduction in X-cell activity and holds sampling density constant for chronic and acute preparations. However, this measure is also affected by the degree of tissue stability, which can vary from moment to moment as a result of vascular pulsation, and by any differences in the integrity (or "health") of the tissue through which passes are made. Therefore, a conclusion which is no less tenable is that sampling density, in combination with relative encounter rates, is an inadequate measure of differential X- and Y-cell activity. Fukada and Stone (1976) provided a more direct demonstration of facilitation of Y-cell activity, in response to a range of stimuli that are similar to those modified by monocular paralysis. However, in view of the findings consistent with the X-suppression hypothesis, it is unlikely that an hypothesis of Y-facilitation by itself, will account for the monocular paralysis effect.

3) Combined X-suppression and Y-facilitation: While the research concerning the effects of binocular stimuli upon LGN physiology does not support an exclusive X-suppression or Y-facilitation hypothesis, it does suggest that there could be a combination of the two underlying the X/Y ratio reduction after chronic paralysis (Fukada & Stone, 1976; Garraghty et al. 1982). Thus, although X-cell suppression may account for the majority of the X/Y ratio reduction in this preparation, some portion of this reduction may be attributable to a facilitation of Y-cell activity.

4) X-response distortion: The rationale for discounting distortion of X-cell functional properties as an explanation for the chronic monocular paralysis effect, though not definitive, is quite compelling.

Garraghty et al. (1982) presented evidence that supports a high degree of relationship in both acute and chronic monocular paralysis preparations, between conduction velocity and receptive field properties for layer A (receiving input from the paralyzed eye). This result argues against the possibility that a breakdown in the ordinarly present systematic relationship in X-cells, between CV (which must be invariant, due to its morphological basis) and receptive field properties, leads to misidentifying X-cells as Y-cells, and thus, to the mistaken impression that the encounter rate for X-cells is reduced after chronic paralysis.

5) Y-afferent unmasking: While the above analysis to some extent appears to discount X-response distortion, it does not even address the possibility that monocular paralysis unmasks ordinarily impotent Y-ganglion cell inputs to LGN X-cells. Since Y-afferents have, on the average, twice the conduction velocity of X-afferents (Fukada & Stone, 1976; Cleland, Levick, Morstyn, & Wagner, 1976; Schroeder, Salinger, & Garraghty, 1982), an active Y-input to an X-cell would totally obscure any X- properties (except with certain forms of stimulation, e.g., bar gratings of high spatial frequency). This would cause LGN X-cells to become Y-like in functional terms and give rise to an apparent reduction in the LGN X/Y ratio. The notion of Y-afferent unmasking runs counter to the prevailing view, based upon both physiological studies (Cleland et al., 1976) and physiological/anatomical studies (Friedlander, Lin, Stanford, & Sherman, 1981) that excitatory activity in X- and Y-channels is functionally segregated until it reaches visual cortex (see Lennie, 1980, for an in-depth discussion). However, it deserves consideration in view of the fact that X/Y interactions have not been

directly studied in the context of monocular paralysis, which clearly does rearrange some of the functional attributes of the retinogeniculate projection system (Salinger et al., 1977a, 1977b; Salinger, Garraghty, & Schwartz, 1980; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Garraghty et al., 1982), and thus could reveal previously undetected components of retinogeniculate physiology.

Purpose of the Present Study

The purpose of the present study was to provide a more definitive picture of the physiological consequences for X- and Y-cells, of activation of the monocular paralysis mechanism. Ideally, to accomplish this aim, one would establish contact with an LGN cell in the acute phase of monocular paralysis, obtain a battery of functional measures, then maintain contact into the chronic phase of paralysis, so as to detect any change in the cell's functional properties. This ideal procedure, if it were repeated for a large number of LGN cells, would be sensitive to X-suppression, Y-facilitation, combined X-suppression and Y-facilitation, X-response distortion, and Y-afferent unmasking. However, this approach is presently impossible, since one could not hope to remain in contact with even one cell for the two weeks it would take for the monocular paralysis effect to become established, let alone repeat the process for the number of cells necessary to fully analyze this effect. Therefore, an approximation, based upon the results of Garraghty et al. (1982) was adopted. Garraghty et al. (1982) reported that while in acute paralysis, anesthesia induction has no impact upon the X/Y ratio; in chronic paralysis, anesthesia induction produces an increase in the X/Y ratio from the reduced value characteristic of

chronic paralysis/unanesthetized to a value characteristic of acute paralysis/unanesthetized. This result suggests that chronic paralysis/anesthetized and acute paralysis may be equivalent, in terms of their impacts upon the X/Y ratio. This in turn suggests that approximation of the ideal analysis is possible, using chronic paralysis/anesthetized as a model for acute paralysis. That is, the properties of individual X- and Y-cells could be examined under both chronically paralyzed and chronically paralyzed/anesthetized (acute analogue) conditions. Thus, instead of having to focus on changes produced by the transition from acute to chronic paralysis, one can focus instead on the changes associated with the transition from chronic paralysis/anesthetized to chronic paralysis/unanesthetized.

Close scrutiny of the results and methods of Garraghty et al. (1982) revealed three potential problems for the use and interpretation of chronic paralysis/anesthetized, as a model for acute paralysis. These problems stem from the choice (by Garraghty et al., 1982) of sodium pentobarbital as an anesthetic, and from the use of data collection procedures vulnerable to the intrusion of error variance from two sources: between-subjects variance and tissue variance (both explained below).

First, pentobarbital anesthesia, achieved by intraperitoneal injection, requires at least 10-15 minutes for induction, and a minimum of several hours for recovery. When achieved with intravenous injections, pentobarbital anesthesia requires only minutes to induce, but requires an hour or more for recovery, particularly after repeated doses. Thus the time necessary for one cycle of anesthesia (induction

plus recovery) exceeds even an optimistic estimate of the time that a single LGN unit, in an unparalyzed subject, can be held under observation (approximately 1/2 hour).

Second, in Garraghty et al. (1982), data collection within the chronic paralysis/anesthetized condition involved recording cells from a number of chronically paralyzed, anesthetized cats. These data were then compared to data similarly obtained from other animals that were chronically paralyzed, but unanesthetized. Because of this comparison procedure, variation in the X/Y ratio due to anesthesia was contaminated by between-subject variance.

Third, tissue variance also could have distorted the results of Garraghty et al (1982). The term "tissue variance" refers to variation in the X/Y ratio that results when data are recorded from passes made in different locations in the LGN. For example, in a relatively extreme case (i.e., when data are compared from passes in excess of 0.5 mm distance from one another in the LGN), a systematic type of tissue variance, retinal eccentricity effects, can be identified. Increasing retinal eccentricity (or increasing distance of recording site from the area of the LGN representing the center of visual space) reduces the X/Y ratio (Hoffmann, Stone & Sherman, 1972). However, even when comparison passes are made at the smallest stereotaxically practical distance from one another (approximately 0.2 mm), tissue variance is observed in the form of a statistical fluctuation (apparently unsystematic) in the X/Y ratio.

Error variance from both of these sources may have affected the apparent strength of the anesthesia-induced increase in the chronic X/Y

ratio in Garraghty et al. (1982). More importantly, it is possible that error stemming from either between-subject variance or tissue variance somehow obscured systematic anesthesia effects upon the X/Y ratio, that might actually be present in acute paralysis. If anesthesia per se were found to have an impact upon the X/Y ratio, it would be a matter of great interest to vision researchers, most of whom regard the deeply anesthetized, systemically paralyzed animal as a "normal" preparation. However, detection of systematic anesthesia effects upon the acute X/Y ratio would complicate the interpretation of results obtained with chronic paralysis/anesthetized as a model for acute paralysis, since a simple interpretation requires that anesthesia impacts upon the X/Y ratio in chronic, but not in acute animals (see Garraghty et al., 1982).

In view of these three concerns--duration of anesthetic effect, between subjects variance, and tissue variance--a number of preliminary steps had to be undertaken before approximation of the ideal analysis could proceed. These were 1) an attempt to produce anesthetic induction and recovery times which allow for at least one complete anesthesia cycle (induction/recovery/induction, or vice versa) during one half-hour period, and which, according to our observations, is the maximum time that we can expect to maintain contact with the average LGN cell; 2) inclusion of a data collection method identical to that of Garraghty et al. (1982), to permit comparison between the results of this study and those of Garraghty et al. (1982); 3) the use of another data collection procedure that is in some respects similar to that of Garraghty et al. (1982), but which reduces the effects of tissue

variance and eliminates those of between-subject variance, and which allowed a more accurate assessment of both the degree to which anesthesia increases the X/Y ratio in chronic animals, and of the possibility of systematic anesthesia effects upon the acute X/Y ratio; and 4) the development of an approach to data collection that represents a close approximation of the ideal experiment, in order to provide a more definitive analysis of the fate of X- and Y-cells after chronic monocular paralysis. Thus, this study actually consists of three experiments: a replication of Garraghty et al. (1982), but using a different, shorter-acting anesthetic; an extension of Garraghty et al. (1982); and an approximation of the ideal analysis.

CHAPTER II

METHOD

This study consisted of three experiments. The first, a partial replication of Garraghty et al. (1982), was an attempt to determine if nitrous oxide anesthesia can produce a reversal of the reduction in the X/Y ratio after chronic monocular paralysis, like the reversal observed with pentobarbital anesthesia. The methods of data collection and anesthesia induction in this experiment allowed a comparison between the effects of nitrous oxide anesthesia and of pentobarbital anesthesia (in Garraghty et al., 1982), despite the difference in duration of effect.

The second experiment, paired pass, attempted a more refined assessment of the magnitude of the increase in the chronic X/Y ratio, associated with anesthesia induction. A second and perhaps more important purpose in this experiment was to reassess the possibility of an anesthesia effect upon the <u>acute</u> X/Y ratio. The methods in the second experiment promoted these aims through complete elimination of between-subject variance, and through drastic reduction of tissue variance.

The third experiment, within-cell, attempted an approximation of an ideal experimental analysis of the fate of X- and Y-cells in chronic monocular paralysis. This approximation was achieved by isolating LGN cells in chronically paralyzed animals and recording any change in a cell's functional properties between the chronic condition and the chronic/anesthesia (the acute analogue) condition.

In all three experiments, the effects of anesthesia per se were assessed in the comparison between acute paralysis anesthetized and acute paralysis/sedated (which has a normal LGN X/Y ratio). Any effects of anesthesia upon the X/Y ratio, in the absence of chronic paralysis effects upon the X/Y ratio, would have been evident in this comparison.

Subjects, Surgical Preparation, and General Recording Procedures

Eleven adult cats, normally reared with respect to visual input, were obtained from a local source for use in these experiments. In order to minimize the number of animals required to conduct this series of experiments, we attempted, where possible, to use each cat as a subject in all three experiments. This approach was possible, since all three experiments required identical surgical preparation, and was actually advantageous from a design perspective, since for each subject, any results obtained with the rather radical methods of Experiments 2 and 3 could be interpreted in the context of a rich background of data obtained with more standard techniques. After inoculation and quarantine, all cats underwent surgical preparation for LGN single-unit recording using previously reported methods (Salinger et al., 1977a; Salinger, Garraghty, & Schwartz, 1980). Under anesthesia, induced with an intraperitoneal injection of a mixture of acepromazine maleate (2.9 mg/kg) and sodium pentobarbital (15.0 mg/kg), the left eye of each cat was immobilized by transection of cranial nerves III, IV, and VI. Six animals were recorded within four days of paralysis (acute monocular paralysis - AcMP). Monocular paralysis in the acute phase (less than four days duration) produces no changes in the relative encounter rates

for LGN X- and Y-cells (Salinger et al., 1977a; Salinger, Garraghty, & Schwartz, 1980; Garraghty et al., 1982), and serves as an alternative to the use of systemic paralysis. Five animals were recorded at greater than 13 days (chronic monocular paralysis - ChMP).

At the designated time for each condition, each animal was prepared for LGN single-unit recording. After resection of the overlying tissue, the skull was implanted with anchoring screws, around which a dental acrylic pedestal was built. Three bolts, set in the acrylic and affixed to a device for mating the pedestal to a stereotaxic headholder, eliminated the need for potentially painful eye, mouth, and ear bars, otherwise necessary for holding the cat's head in the appropriate position with respect to the stereotaxic plane during recording. Craniotomies were made over the right optic chiasm, optic tract, and LGN, to permit electrode access to these structures.

A bipolar stimulating electrode (stainless steel, teflon coated) was positioned 2.0 mm lateral to the anterior-posterior center of the optic chiasm, as defined by electrophysiological mapping. This mapping procedure is critical for this analysis, since it drastically reduces between-animal variability in mean OX latency. An additional electrode of identical construction was placed in the optic tract (OT) approximately 10.0 mm postero-lateral to the OX placement. The placement of each electrode was histologically verified after data collection was completed for each subject.

To permit the induction of nitrous oxide anesthesia, the tissue overlying the trachea was retracted, and a cannula (12 ga., teflon) inserted into the trachea. Gases were then delivered to the animal in

the appropriate mixture for anesthesia, using a gas anesthesia apparatus (Ohio Chemical and Surgical Co.). When recovery from anesthesia was required, the gas flow was terminated, allowing the animal's unimpaired respiration to promote rapid recovery. The animals were allowed to recover from anesthesia after surgery, but during daily recording sessions were sedated (intraperitoneal injections of acepromazine, 2.9 mg/kg, and pentobarbital, 5.0 mg/kg) sufficiently to produce acceptance of the painless head restraint used (e.g., Orem et al., 1973) in semichronic single unit recording. The animals were guarded against discomfort during the experiment by the fact that they were not physically restrained during recording (except for the head), and collection of data could not proceed if the subject was moving about in response to discomfort, pain, or even restlessness.

At the beginning of each recording session, the animal was sedated, placed in the stereotaxic device, and the optic disk position for the paralyzed eye was plotted on a tangent screen at 1.5 m. from the orbit. Locations of receptive fields for LGN cells encountered were then plotted with respect to this landmark (Fernald and Chase, 1971), and only data for cells with receptive fields in the central ten degrees of visual space entered into the analyses. Plano contact lenses were used to protect the eyes from dessication during recording sessions.

LGN single units were located through their tendency to phase-lock with light stimuli, flashed in the animal's eyes at regular intervals, or by their response to moving gratings, hand-held wands, or electrical stimulation of the optic chiasm and optic tract. Then, single-unit activity was recorded with tungsten microelectrodes (Haer instruments),

with impedances between 50 and 100 megohms at 1000 hz. Action potentials were amplified with a WPI DAM-5 preamplifier and a Grass A-C amplifier, and identified according to the criteria of Bishop, Burke and Davis (1962).

Independent Variables

1) Manipulation of anesthesia state. Since anesthesia was an independent variable in this study, it was continuously monitored and maintained at one of two levels. The first level, lightly sedated, was defined by the presence of conjoint (abdominal and thoracic) instigation of breathing, a well defined and robust paw withdrawal reflex, palpebral (or eyeblink) reflexes, sensitivity to pain, periodic spontaneous physical activity, and the capacity for normal feeding and ataxic locomotion upon release from head restraint. This state is standard to our recording procedures and is induced by intraperitoneal injections of a mixture of acepromezine maleate (2.9 mg/kg) and sodium pentobarbital (5.0 mg/kg). The second level, deeply anesthetized, was defined by the presence of abdominal instigation of breathing and by the absence of withdrawal and palpebral reflexes. These criteria are consistent with conventional definitions of anesthetic state (e.g., stage III, plane 2 of Cohen, 1975). After sedation of the animal with an intraperitoneal injection of a mixture of acepromazine maleate (of 2.9 mg/kg) and pentobarbital (5.0 mg/kg), anesthesia was induced by inhalation of a mixture of nitrous oxide and oxygen (80% nitrous oxide and 20% oxygen). Use of nitrous oxide anesthesia permitted rapid induction and recovery times (5-10 min. in either case), which in turn allowed us to observe individual X- and Y-cells under both anesthetized and unanesthetized

conditions.

Throughout the course of the experiment, the animal's temperature and respiration were continuously monitored and maintained within normal physiological limits. However, since deep anesthesia is associated with an inability to maintain normal temperature and respiration, these vital signs provided additional feedback concerning the animal's state of anesthesia.

2) Duration of monocular paralysis. The second independent variable in this study was duration of monocular paralysis, with two levels: 1) acute monocular paralysis (AcMP), which requires that all data be collected within four days of the paralysis, and is taken to represent the normal preparation (see above); 2) chronic monocular paralysis (ChMP), a condition which requires that data collection commence at no less than 14 days post-op. Chronic monocular paralysis results in a profound reduction in the LGN X/Y ratio, the "underpinnings" of which are the focus of this investigation. The levels of the second independent variable were completely crossed with those of the first, such that data recorded from both AcMP and ChMP animals appeared in both anesthetized and unanesthetized conditions.

Dependent Measures I: Measurement of the LGN X/Y Ratio

Conduction velocity. For each cell encountered in the LGN contralateral to the paralyzed eye, we measured onset latencies of response to optic chiasm and optic tract stimulation using the methods of Hoffmann et al. (1972). Then, using histologically confirmed measures of the stereotaxic distance between the OX and OT electrodes, we were able to compute conduction velocity for each axon (Schroeder et

al., 1982).

Receptive field properties. In addition to obtaining OX latency and CV measurements from each cell, a subset of the cell sample obtained here (all cells in lamina A, which is innervated by the paralyzed eye) was classified as X- or Y-type on the basis of four receptive field measures: 1) receptive field center diameter (X < 1.0 retinal degrees; Y > 1.0 degrees); 2) response to moving gratings (X, inhibited by high grating velocity at higher spatial frequencies; Y, burst responding to high grating velocity); 3) response to a rapidly moving center-inhibiting stimulus larger than the receptive field center (X, no response; Y, response); and 4) degree of center-surround antagonism (X, strong antagonism; Y, weak or absent antagonism) (Hoffmann et al., 1972; Wilson, Rowe, & Stone, 1976; Kratz, Webb, & Sherman, 1978; Bullier, & Norton, 1979).

Cell classification. The receptive field measures outlined above, in conjunction with OX latency and CV, yield a classification battery of six tests, and cells were classified as X- or Y-type if no more than one test disagreed with the others. Cells which could not be classified by these criteria were excluded from the analyses. Since receptive field analysis could not be conducted for units in lamina A1, which is driven by the mobile eye, lamina A1 units were classified on the basis of CV alone (see Garraghty et al., 1982). Classification of each cell encountered in a given electrode penetration in either Experiment 1 or 2 yielded a measure of the relative proportions of X- to Y-cells encountered, or an X/Y ratio.

Dependent Measures II: Assessment of Change in Single Unit Characteristics

Receptive field properties. In Experiment 3, for each cell encountered in lamina A (innervated by the paralyzed eye), the receptive field properties were measured in each anesthesia condition. Such repeated measurement of these properties provided an assessment of their stability across anesthesia conditions (relating to the X-response distortion and the Y-afferent unmasking hypotheses).

Axon time and synapse time. In order to evaluate the impact of chronic monocular paralysis, and of anesthesia upon individual cells' electrophysiological properties in the region of the retinogeniculate synapse, two additional measures were computed (for each cell), which depend in part upon the CV of the axon providing input to that cell. The CV of an axon were used, together with the histologically determined distance from the optic chiasm to the LGN, to compute the time an action potential required to travel from the optic chiasm to the LGN, or T-AX. Since T-AX is a derivative of and a temporal analogue to CV, any result obtained with measurement of T-AX implies an equivalent result for the CV measure. Subtracting T-AX from OX latency yielded T-SYN or the time required to transmit activation across the synaptic zone (Schroeder et al., 1982). Assessment of the effects of monocular paralysis upon T-AX and T-SYN in individual cells was obtained by comparing T-AX and T-SYN values for the chronic/unanesthetized condition to the corresponding values for that cell in the chronic/anesthetized (acute analogue) condition. For individual cells, change in either axon time or synapse time, unaccompanied by change in receptive field classification, was

taken to indicate a distortion of cell electrophysiological properties (as in Hypothesis 4). Change in either axon time or synapse time, if accompanied by a congruent change in receptive field classification, was taken to indicate Y-afferent unmasking (as in Hypothesis 5).

Threshold of response to optic chiasm stimulation. After a cell's OX latency was identified, the threshold at which stimulation yields a reliable response (OX threshold) was also measured, in terms of stimulus voltage x stimulus pulse duration (or volt-sec). These threshold measures yielded an assessment of change in the excitability (facilitation or suppression) of individual X- and Y-cells, related to anesthesia induction, in both acute and chronic paralysis conditions.

Specific Data Collection Procedures

As mentioned earlier, use of nitrous oxide anesthesia, due to its extremely rapid induction and recovery times, made it possible to approximate the ideal analysis (recording from individual LGN cells under both acute and chronic paralysis conditions), substituting chronic paralysis/anesthetized for acute paralysis. However, since it has not yet been demonstrated that in the context of acute and chronic paralysis, the impact of nitrous oxide anesthesia is equivalent to that of pentobarbital anesthesia, this question was addressed in a preliminary experiment (see Experiment 1 below). Another preliminary experiment was conducted to assess the degree to which between-subjects variance and tissue variance (see above) may have affected the results of Garraghty et al. (1982). This experiment (Experiment 2, see below) was undertaken to address the possibility that error variance from either or both of these sources may have obscured subtle anesthesia

effects in acute animals.

Experiment 1. Data were collected in the first experiment using methods identical to those of Garraghty et al. (1982). For each animal, a maximum number of cells were recorded in each of a number of electrode passes through the LGN. Data for each of the four paralysis/anesthesia conditions were then combined across passes, and across animals. This procedure permitted comparison of the pattern of results obtained in the present study, with that of Garraghty et al. (1982), to determine if the effects of nitrous oxide anesthesia (present study), in the context of both acute and chronic monocular paralysis, are the same as the effects of the systemic pentobarbital anesthesia used by Garraghty et al. (1982). Data analysis was conducted using a nonparametric analysis, the Mann-Whitney U test (Daniel, 1978), with subject as the unit of observation.

Experiment 2. Data were collected in the second experiment, utilizing a paired-pass technique, which involved simply making an electrode pass through the LGN, retracting the electrode to the lateral ventrical just above the LGN, then penetrating once again through the same electrode track, with data being recorded from each cell encountered in each pass. Anesthesia state was manipulated within pass-pairs, such that one sampling pass of the pair was collected with the subject unanesthetized and the other collected from virtually the same tissue, with the subject deeply anesthetized (with the order counterbalanced). The power of this technique stems from the fact that it allows assessment of the impact of anesthesia state upon the X/Y ratio, with less intrusion from tissue variance, and permits rapid and

efficient assessment of the acute (normal) or chronic (reduced) nature of the X/Y ratio in a given subject. Tissue variance is reduced or even eliminated in paired-pass, by the practice of withdrawing the electrode into the lateral ventrical, above the LGN, but leaving it well within the brain, to maximize the probability of re-entering the same tissue, if not recording from the same cells. Reduction of tissue variance is important here, since it minimizes variation in the X/Y ratio, independent of monocular paralysis and anesthesia effects. The efficiency aspect of the paired-pass was also advantageous here since in Experiment 3, it permitted interpretation of any anesthesia-related changes within individual cells, in the context of an animal that is known to have either a normal or reduced X/Y ratio. Since paired-passes are related samples, statistical analysis of the results of Experiment 2 were conducted using a nonparametric test for paired observations, the Wilcoxon matched-pairs signed-ranks test (Daniel, 1978). Difference scores, which form the basis for this test, were computed between the members of a paired-pass unit.

Experiment 3. The same animals that were used in Experiments 1 and 2 also served in Experiment 3. Along with its ethical and practical advantages, such multiple usage allowed interpretation of any changes found in the properties of individual units in Experiment 3, in the context of a known X/Y ratio. Confirmation of the acute or chronic state of the X/Y ratio, while not absolutely necessary, is beneficial, since Experiment 3 is an attempt to elucidate the types of plasticity in functional properties that could provide a basis for the differences in X/Y ratio terms between acute and chronic paralysis. Data collection in

the third experiment involved penetrating to the LGN, then isolating single units with the animal either anesthetized or unanesthetized, as defined above (alternating order). Once a unit was isolated, and all dependent measures obtained, the animal's anesthesia state was reversed, and all measures repeated on the same cell. Finally, the original state of anesthesia was be re-introduced, and all measures taken once again. As in Experiment 2, the statistical comparisons in this experiment were performed between related samples. Therefore, the results of this experiment were also analyzed with nonparametric tests for related samples.

There were two principal difficulties associated with the within-cell approach. First, although pilot studies indicated that rapid induction and reversal of anesthesia with nitrous oxide is feasible, pilot work also suggested that repeated cycling of anesthetic state may be sufficiently stressful as to compromise the health of the subject. The response to this concern was a continuous, detailed monitoring of all vital signs, the immediate institution of corticosteroid (dexamethasone) therapy at the first sign of incipient difficulties, and termination of recording if steroid therapy did not abate the problem.

The second principal difficulty in Experiment 3 was that of maintaining contact with a given cell long enough to obtain a complete set of measurements. Complete measurement for a given cell entails isolating the cell, maintaining contact with it through all three phases of anesthesia manipulation, and conducting measurements in each phase, in the face of continuous pulsatile movements of the brain, periodic

subject restlessness, coughing that often accompanies the initiation or termination of gas flow into the trachea (for anesthesia manipulation)--all of which can result in electrode slippage and loss of the cell under observation.

Since certainty in this regard was essential if the within-cell procedure was to yield a credible analysis, two procedures were rigidly adhered to. First, the activity of each cell under study was continuously monitored through both auditory and visual displays of its action potentials throughout all phases of anesthesia manipulation, and consensus amongst all experimenters present, regarding the identity of the cell in terms of its waveform and "signature response" to stimulation, was required. Cells whose continued isolation and identity was uncertain were excluded from the analyses. Second, given that a cell qualified in the above sense, if any change (for any dependent measure) occurred between phases 1 and 2 (anesthetized to unanesthetized, or vice versa) that was not reversed in phase 3 (re-institution of the initial anesthesia state), the cell in question was designated as one that shows a nonreversing change. Nonreversing changes were taken as indicative of an anesthesia-related lability, as opposed to a systematic sensitivity to anesthesia state. Cells showing nonreversing changes were therefore not included in any presentation of results which concerned systematic anesthesia effects upon cell properties. Thus, a conservative approach was adopted, and while it assured a credible analysis of the data that were obtained, it by no means guaranteed that potentially useful information was not discarded.

CHAPTER III

RESULTS

In all three experiments, acute and chronic monocularly paralyzed subjects were interleaved in the sequence of data recording. This practice was intended to address the concern that improvement in the technical capacities of the experimenters over the course of the study produced a change in practice, or in judgement criteria, that might have had a differential impact upon results obtained from chronic and acute subjects.

Experiment 1

Data were collected from 144 cells encountered in LGN laminae A and A1 of six acute monocularly paralyzed cats. Of these, 76 units were recorded with the subject unanesthetized, and 68 were recorded with the subject anesthetized. Data were also collected from 202 cells in LGN laminae A and A1 of five chronic monocularly paralyzed cats: 100 with the subject unanesthetized; 102 with the subject anesthetized.

Each acute and chronic cat was recorded under both anesthetized and unanesthetized conditions, and data were collected for each of these conditions in a series of adjacent electrode penetrations through the LGN. Anesthesia state was held constant during each penetration, but was alternated between anesthetized and unanesthetized conditions, from one penetration to the next (order counterbalanced). Each cell encountered was classified as X- or Y-type with the exception of seven

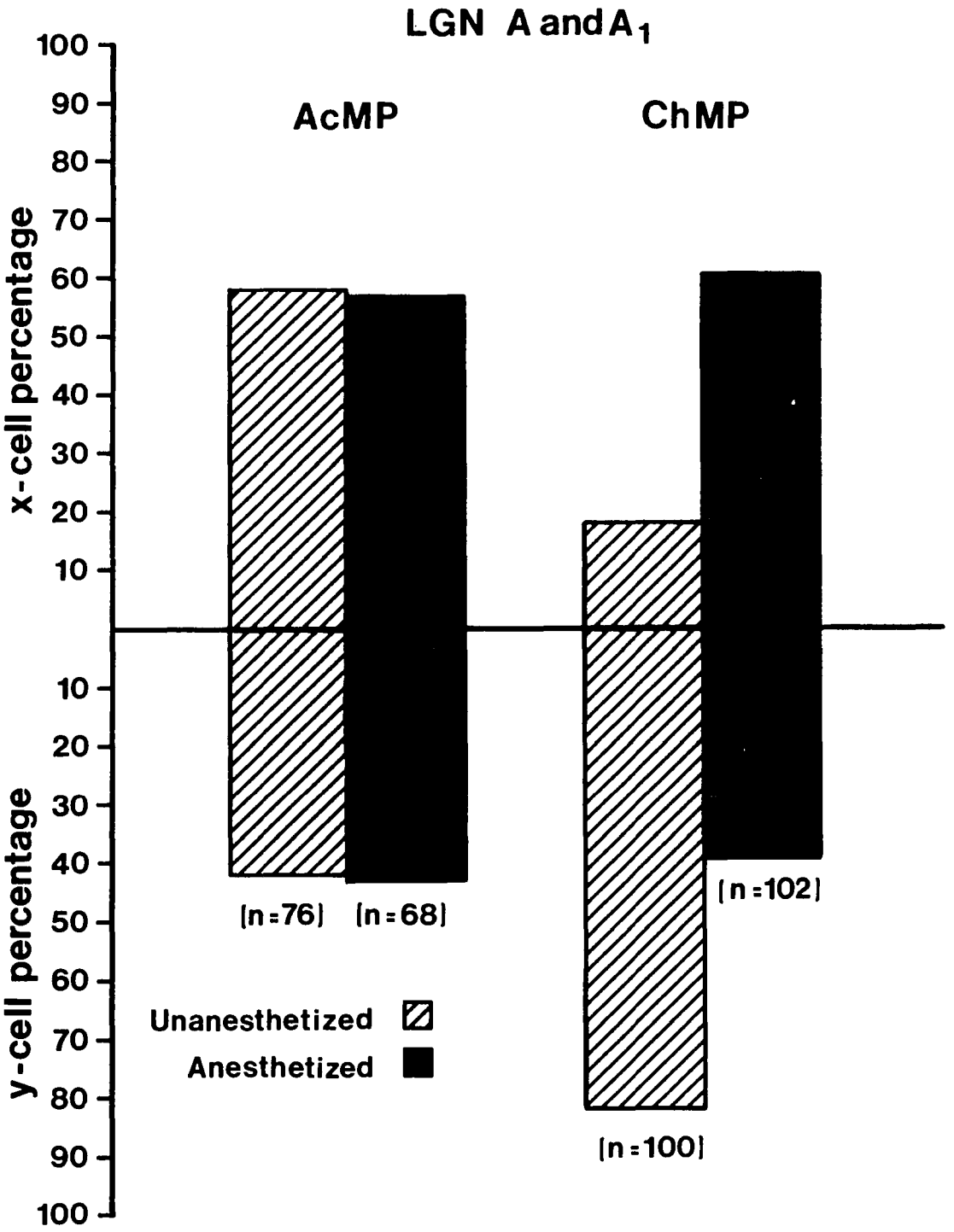
units (three in acute animals, four in chronic animals), which exhibited mixed properties and were excluded from the analyses.

Figure 1 displays the percentage of cells classified as X-type (% X-cell, top) and Y-type (% Y-cell, bottom) out of the total sample recorded in LGN laminae A and A1, of acute (AcMP, left side) and chronic (ChMP, right side) monocularly paralyzed animals. Since this experiment was an attempted replication of the anesthetic reversal effects noted by Garraghty et al. (1982), three facets of the results are critical. First, chronic paralysis/unanesthetized resulted in a 69% reduction (acute X-cell percentage minus chronic X-cell percentage, divided by acute X-cell percentage) in X-cell percentage and a 95% increase (computed in the same way as X-cell percentage change) in Y-cell percentage, relative to acute paralysis/unanesthetized. Data recorded from each of the individual subjects were consistent with this grouped pattern (see Appendix A). Thus, when data were recorded with the subject unanesthetized, a chronic (two week) duration of monocular paralysis produces a severe reduction in the X/Y ratio (AcMP/unanesthetized vs ChMP/unanesthetized, M-W $p<.025$). This effect corresponds to that reported in earlier studies (Brown and Salinger, 1975; Salinger et al., 1977a; Garraghty et al., 1982).

The second critical aspect of these results, in relation to those of Garraghty et al. (1982), is the fact that nitrous oxide anesthesia, like the pentobarbital anesthesia used in the earlier study, had no impact upon the X/Y ratio in acute monocularly paralyzed subjects. The X- and Y-cell percentages observed in acute paralysis/unanesthetized

FIGURE 1

Percentages of X-cells (top) and Y-cells (bottom) encountered in series of electrode penetrations through LGN laminae A and A1 (central 10 degrees) of acute (AcMP - left) and chronic (ChMP - right) monocularly paralyzed cats. Cross-hatched bars represent data recorded from unanesthetized subjects. Dark bars represent data recorded from subjects anesthetized with nitrous oxide. N's refer to total number of cells in each monocular paralysis/anesthesia condition.


LGN A and A1
AcMP
ChMP
x-cell percentage
y-cell percentage
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
60
70
80
90
100
(n=76)
(n=68)
(n=102)
(n=100)
Unanesthetized
Anesthetized

(X-cell: 57.9%; Y-cell 42.1% - Figure 1) were virtually unchanged by the induction of nitrous oxide anesthesia (X-cell: 57.4%; Y-cell: 42.6%). Again, data recorded from each individual subject were consistent with this grouped pattern (see Appendix A). Thus, the results of acute paralysis/unanesthetized and acute paralysis/anesthetized were not significantly different (AcMP/unanesthetized vs AcMP/anesthetized, M-W $p>.05$). The fact that acute paralysis/anesthetized did not differ significantly from acute paralysis/unanesthetized suggests that in animals with a normal X/Y ratio, nitrous oxide anesthesia per se has no significant impact on the X/Y ratio.

The final point of concern in regard to a replication of Garraghty et al. (1982) is that anesthesia effects, while not evident in acute monocularly paralyzed animals, were quite prominent in chronic monocularly paralyzed animals. Figure 1 (right side) displays the X- and Y-cell percentages obtained from chronic paralysis/anesthetized animals (X-cell: 60.8%; Y-cell 39.2%) relative to that of chronic paralysis/unanesthetized (X-cell: 18.0%; Y-cell: 82.0%). The 238% increase in X-Cell percentage in chronic paralysis/anesthetized, relative to chronic paralysis/unanesthetized, along with the corresponding decrease in Y-cell percentage (Figure 1, right), suggests that the induction of nitrous oxide anesthesia reversed the impact of chronic monocular paralysis upon the X/Y ratio, increasing the X/Y ratio to the level observed in acute monocular paralysis (unanesthetized or anesthetized). Statistical analysis confirmed this impression, since chronic paralysis/anesthetized was significantly different from chronic

paralysis/unanesthetized (ChMP/anesthetized vs ChMP/unanesthetized, M-W $p<.037$), but was not significantly different from acute paralysis/unanesthetized (ChMP/anesthetized vs AcMP/unanesthetized, M-W $p<.500$), or from acute paralysis/asesthetized (ChMP/anesthetized vs AcMP/anesthetized, M-W $p<.155$). This pattern of results was obtained in all animals (see Appendix A).

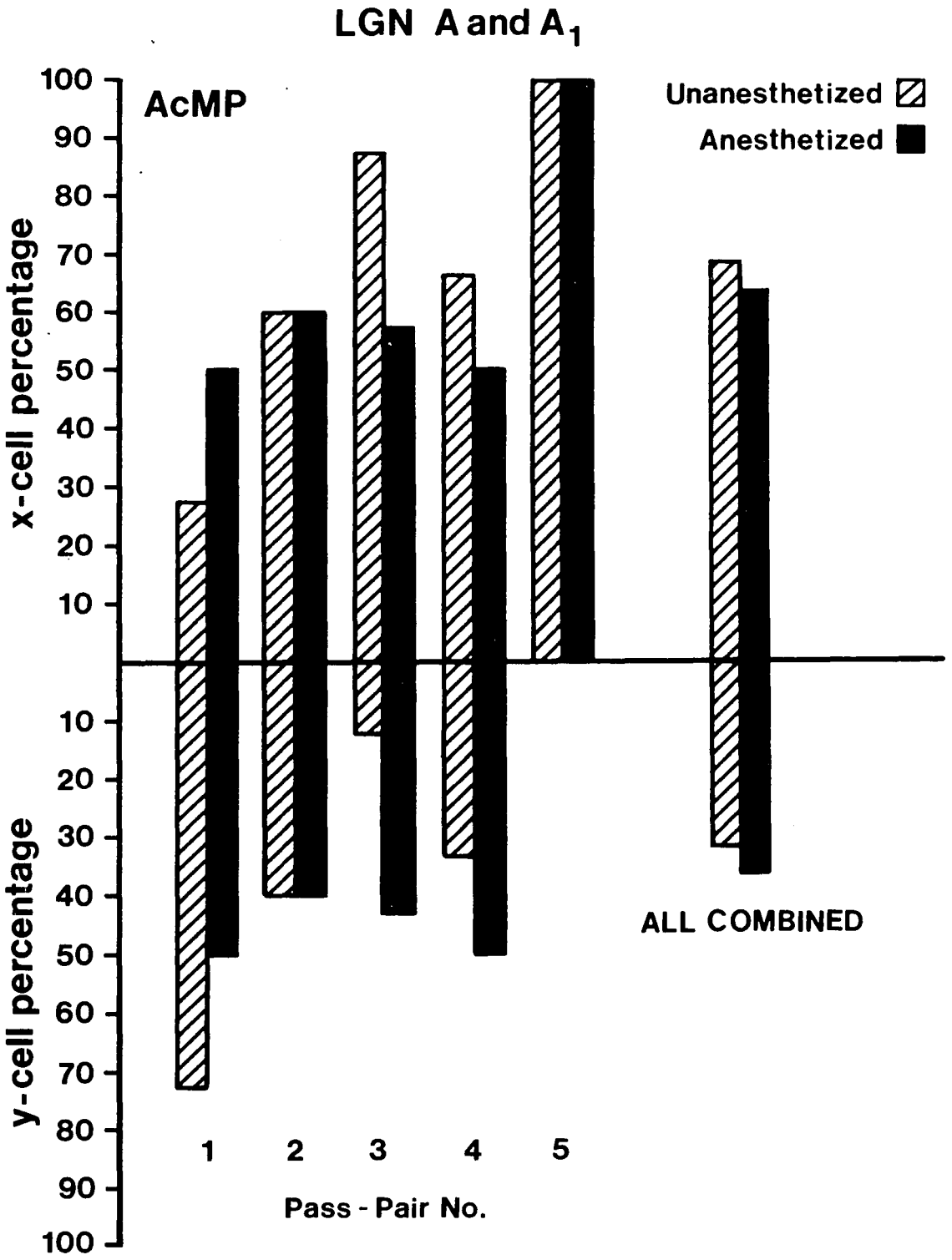
Thus, anesthetizing subjects with nitrous oxide, during data recording, has a systematic impact upon the X/Y ratio in chronic but not in acute monocularly paralyzed animals. In chronic animals, the induction of anesthesia promotes an increase in the X/Y ratio, relative to that recorded with the subject unanesthetized.

Experiment 2

The data-gathering methods in Experiment 2 (paired-pass) provided an opportunity to assess the impact of anesthesia upon the X/Y ratio, while eliminating between-subject variance and drastically reducing tissue variance (see methods). Data were collected in paired-passes from five acute monocularly paralyzed cats, one pass of the pair conducted with the cat unanesthetized, the other, in the same electrode track, with the cat anesthetized (order counterbalanced). These data, displayed in Figure 2, demonstrate that while in three of the five paired-passes, there was a change in the X/Y ratio associated with anesthesia induction, the direction of this effect was not consistent. In one case, anesthesia induction increased the X-cell percentage, and in two cases, anesthesia decreased the X-cell percentage. Further, in two out of the five pass-pairs, the X-cell percentage value was identical

FIGURE 2

Percentages of X-cells (top) and Y-cells (bottom) recorded in paired passes (numbered 1-5 at bottom) through LGN laminae A and A1 (central 10 degrees) of acute monocularly paralyzed cats (AcMP). In each pair, the cross-hatched bar represents data obtained from a single electrode penetration while the subject was unanesthetized, and the dark bar represents data obtained from another penetration in the same track through the LGN, while the subject was anesthetized (order counterbalanced). The data from all unanesthetized passes and from all anesthetized passes are grouped at the far right. The number of cells per pass ranges from 4-16.


LGN A and A1
AcMP
Unanesthetized
Anesthetized
x-cell percentage
y-cell percentage
100
90
80
70
60
50
40
30
20
10
1
2
3
4
5
ALL COMBINED
Pass - Pair No.

for both anesthesia conditions. As a result, when the X-cell percentages for all passes in acute paralysis/unanesthetized and in acute paralysis/anesthetized were averaged and compared (Figure 2 - extreme right), the difference between the two conditions was slight (AcMP/unanesthetized - 68.3% X-cells to 31.7% Y-cells; AcMP/anesthetized - 63.4% X-cells to 36.6% Y-cells), and failed to achieve statistical significance (AcMP/unanesthetized vs AcMP/anesthetized, Wilcoxon $p>.05$).

Paired-pass data collected from four chronic monocularly paralyzed cats (Figure 3) reveal a marked and consistent anesthesia effect. Within each of the seven pass-pairs (order of anesthesia condition counterbalanced across pass-pairs), the induction of anesthesia increased the X-cell percentage. Thus, when the mean X-cell percentage for chronic paralysis/unanesthetized passes was compared to that for chronic paralysis/anesthetized passes (Figure 3 - extreme right), the result was a 266% increase in X-cell percentage (anesthetized relative to unanesthetized), an effect which is statistically significant (ChMP/unanesthetized vs ChMP/anesthetized, Wilcoxon $p<.014$).

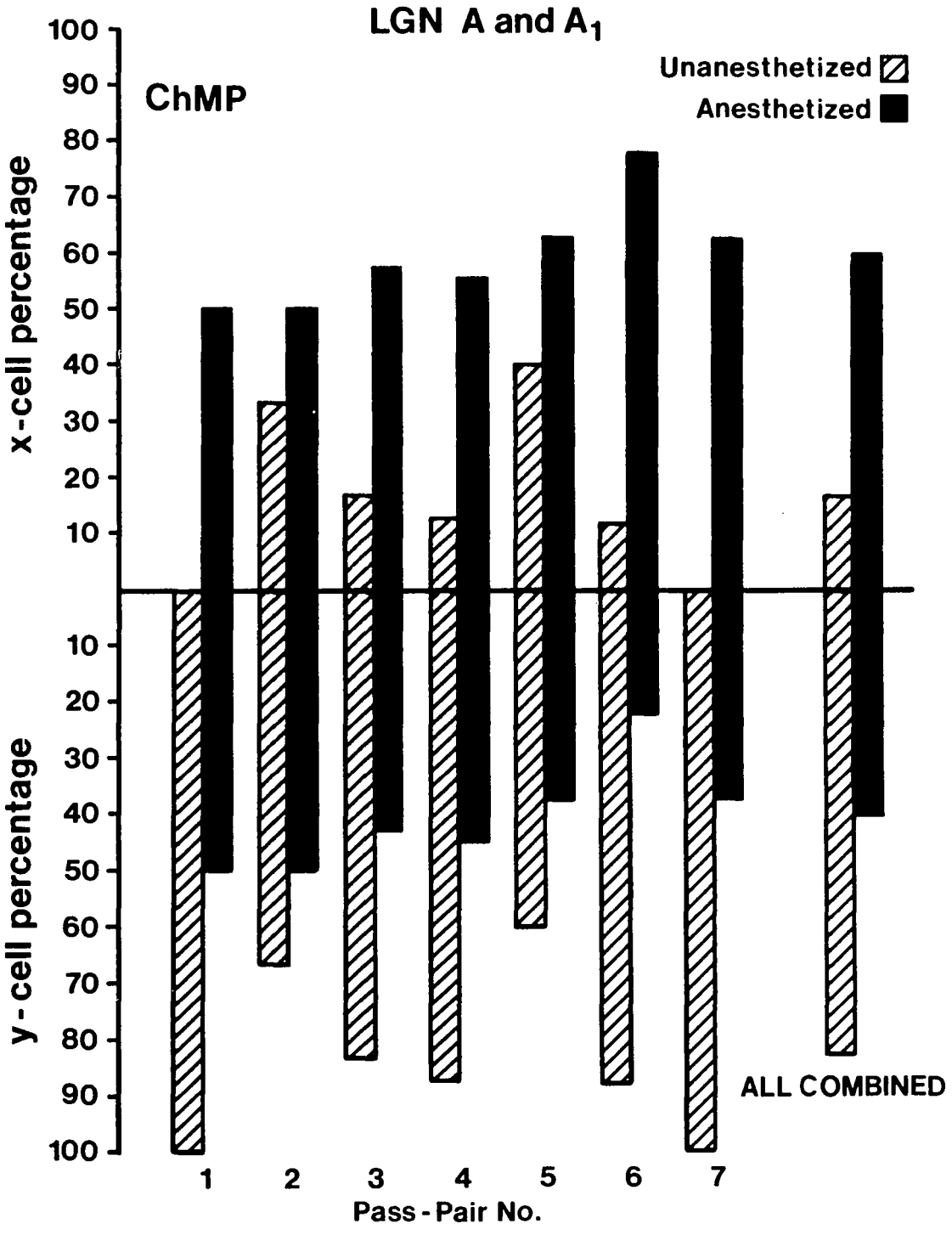
In summary, in this experiment as in Experiment 1, anesthesia did not appear to have a systematic impact upon the X/Y ratio in acute monocularly paralyzed animals. The impact of anesthesia induction in chronic animals in contrast, was a marked and consistent increase in the X/Y ratio.

Experiment 3

This experiment was an attempt to determine the nature of the processes at the level of the single LGN cell, that could underlie

FIGURE 3

Percentages of X-cells (top) and Y-cells (bottom) recorded in paired passes (numbered 1-7 at bottom) through LGN laminae A and A1 (central 10 degrees) of chronic monocularly paralyzed cats (ChMP). In each pair, the cross-hatched bar represents data obtained from a single electrode penetration while the subject was unanesthetized, and the dark bar represents data obtained from another penetration in the same electrode track through the LGN, while the subject was anesthetized (order counterbalanced). The data from all unanesthetized passes and from all anesthetized passes are grouped at the far right. Number of cells per pass ranges from 5 to 10.


LGN A and A1
ChMP
Unanesthetized
Anesthetized
x-cell percentage
y-cell percentage
100
90
80
70
60
50
40
30
20
10
10
20
30
40
50
60
70
80
90
100
1
2
3
4
5
6
7
Pass-Pair No.
ALL COMBINED

the changes in the X/Y ratio caused by manipulation of anesthesia state in chronic monocularly paralyzed animals. The dependent measures were designed to provide sensitivity to processes such as unit suppression or facilitation, unit response distortion, and substitution of afferents (see methods), any of which, logically, could underlie shifts in the X/Y ratio. Each cell that was studied over three anesthesia cycles (anesthetized, unanesthetized, then anesthetized, or unanesthetized, anesthetized, then unanesthetized) fell into one of three categories (see methods) with respect to each dependent measure: 1) It showed no anesthesia effect; that is, it did not change with manipulation of anesthesia state, 2) It showed a reversing change; that is, it changed in one or more functional properties between phases one and two, then reversed toward its initial state in phase three (reinstitution of the original anesthesia condition), 3) It showed a nonreversing change; that is, it changed in one or more functional properties between anesthesia phases one and two, but failed to reverse toward its original state, with the introduction of phase three.

Individual cells were studied under both anesthetized and unanesthetized conditions (order counterbalanced across cells) in four acute monocularly paralyzed cats. Since all of these subjects were used in Experiments 1 and 2, previous data collection confirmed the presence in each animal, of an X/Y ratio that was typical of an acute monocularly paralyzed animal (see grouped data in Figure 1, and paired-passes 2, 3, 4 and 5 in Figure 2, each of which was obtained from one of these subjects). Data were also collected from individual cells under both anesthetized and unanesthetized conditions (order counterbalanced across

cells), in five chronic monocularly paralyzed animals. Four of these animals participated in Experiments 1 and 2, yielding grouped data (see Figure 1) and paired-pass data (see Figure 3) characteristic of chronic animals. Complete measurement for cells in chronic animals, as in acute animals, required measurement of a particular dependent variable in each of the three anesthesia phases.

The size of the sample with complete data collection (i.e. measurement of properties in all three anesthetic phases) varied according to the dependent measure in question. Therefore, the results for each dependent measure will be discussed in turn.

Receptive Field Properties

In acute animals, complete measurement of receptive field properties (i.e. classification of a cell as X- or Y-type in all three anesthesia phases) was accomplished for a total of 20 cells, 10 X-cells and 10 Y-cells. These measurements provided an index of qualitative rather than of quantitative change, since they were sensitive to change in the receptive field classification of a unit, but were insensitive to subtle variation in individual receptive field properties (see methods). In no case was a change in the receptive field classification of a unit (either reversing or non-reversing) observed in acutely paralyzed animals. Thus, the receptive field categorization of all cells with complete measurement of receptive field properties was found to be unaffected by manipulation of anesthesia state.

In chronic animals, complete receptive field measurements were obtained for 27 cells; 14 X-type and 13 Y-type. In the chronically paralyzed condition, as in the acutely paralyzed condition, no reversing

change (related to anesthesia level) in receptive field classification was observed. Only one case of nonreversing change was detected, a Y-cell, which changed to X-type receptive field characteristics under anesthesia, but failed to revert to Y-type when the animal was allowed to recover from anesthesia. Thus, in chronic animals, 0.0% of the population of X- and Y-cells had a reversing change in receptive field characteristics, 2% had a nonreversing change, and 98% were found to be unaffected by anesthesia. Taken together, the acute and chronic results regarding receptive field properties suggest that in a given LGN cell, classification of a cell as X- or Y-type, on the basis of these properties, is insensitive to manipulation of anesthesia state.

Axon Time and Synapse Time

Acute monocular paralysis. Axon time and synapse time are the compartments of OX latency, which itself estimates retinogeniculate conduction time. Complete data (measurement in all anesthesia phases) for these dependent measures were obtained for 57 cells, 28 X-type and 29 Y-type in the acute preparation. Of these, 3 X-cells (11%) showed a reversing change in axon time: In two cells, axon time appeared to increase with anesthesia; in one cell, axon time appeared to decrease with anesthesia. Three acute X-cells (11%) showed nonreversing changes in axon time, and the remaining 22 cells (78%) were unaffected. Only one X-cell (4%) showed a reversing change in synapse time, and in this case, synapse time appeared to decrease with anesthesia. No acute X-cells had nonreversing changes in synapse time, and synapse time was unaffected by anesthesia in the remaining 27 acute X-cells (96%). Out of the acute Y-cell sample, one cell (3%) showed a reversing change in

axon time: a decrease in axon time with anesthesia. Two (7%) showed a nonreversing increase in axon time with anesthesia, and the remaining 26 (90%) were not affected. Two Y-cells (8%) showed a reversing change in synapse time: both increased synapse time with anesthesia, none showed nonreversing change, and 27 (93%) were not affected. No significant pattern of reversing change in axon time or synapse time was found for either X- or Y-cells (X-cells: Tax/anesthetized vs Tax/unanesthetized, Wilcoxon $p>.05$; tsyn/anesthetized vs Tsyn/unanesthetized, Wilcoxon $p>.05$; Y-cells: Tax/anesthetized vs Tax/unanesthetized, Wilcoxon $p>.05$; Tsyn/anesthetized vs Tsyn/unanesthetized, Wilcoxon $p>.05$).

While on a within-cell basis, none of the changes in axon time or synapse time were statistically significant, acute X-cells, as a group, appeared to show a greater degree of lability (i.e., change, reversing, or nonreversing, in any direction) by these measures than acute Y-cells. 25% of acute X-cells as opposed to 17% of acute Y-cells were affected to some degree by the anesthesia manipulation. However, this difference was not statistically significant (M-W $p>.490$).

Although axon time and synapse time in both X- and Y-cells exhibit some degree of anesthetic lability, the lack of reversing changes in these measures suggests that in the vast majority of the X- and Y-cells, axonal and synaptic transmission times are unaffected by nitrous oxide anesthesia (93% unaffected in axon time; 95% unaffected in synapse time). Therefore, it appears that the temporal compartments of retinogeniculate information transmission (axon time and synapse time) are not significantly affected by anesthesia induction in acute monocularly paralyzed animals.

Chronic monocular paralysis. Complete measurements for axon time and synapse time were obtained from 78 cells in chronically paralyzed animals; 35 X-type and 43 Y-type. Of the chronic X-cells, 4 (11%) showed reversing increase in axon time associated with anesthesia induction, 9 cells (26%) showed nonreversing change, and the remaining 22 (63%) were not affected. One chronic X-cell (3%) showed a reversing increase in synapse time associated with anesthesia induction, one (3%) showed an nonreversing change, and 34 (94%) were not affected by the anesthesia manipulation. No X-cells had anesthesia-related decreases in either axon time or synapse time, in chronic animals.

Of the chronic Y-cells, 2 (5%) showed a reversing anesthesia-related change in axon time, with one increasing and the other decreasing, 3 (7%) showed nonreversing change, and 38 (88%) showed no effect. None showed a reversing change in synapse time, one (2%) showed nonreversing change, and 42 (98%) showed no effect. Statistical analysis of these data revealed no significant pattern of reversing anesthesia-related change in axon time or in synapse time for either X- or Y-cells (X-cells: Tax/anesthetized with Tax/unanesthetized, Wilcoxon $p>.05$; Tsyn/anesthetized with Tsyn/unanesthetized, Wilcoxon $P>.05$; Y-cells: Tax/anesthetized with Tax/unanesthetized, Wilcoxon $p>.05$; Tsyn/anesthetized with Tsyn/unanesthetized, Wilcoxon $p>.05$).

In chronic as in acute animals, X-cells appear to demonstrate greater lability (43% of X-cells vs 14% of Y-cells show either reversing or nonreversing changes associated with the anesthesia manipulation), and in the chronic paralysis condition, this difference is statistically significant (M-W, $p<.025$). Further, purely in terms of the lability of

axon time or synapse time, a difference between acute and chronic X-cells was apparent. In acute cats, 25% of X-cells showed anesthesia-related lability, while in chronic cats, 43% of X-cells showed anesthesia-related lability. The difference in lability between acute and chronic X-cells is statistically significant (M-W, $p<.031$). Y-cells, in contrast, showed approximately the same degree of lability in acute (17% showed anesthesia-related lability) and chronic (14% showed anesthesia-related lability) paralysis, a difference which is not statistically significant (M-W, $p>.05$). Thus, while on a within-cell basis, anesthesia induction appeared to have no systematic impact upon either axon time or synapse time (in either cell type or paralysis condition), X-cells per se appear more labile in response to anesthesia, and chronic X-cells are even more labile than acute X-cells.

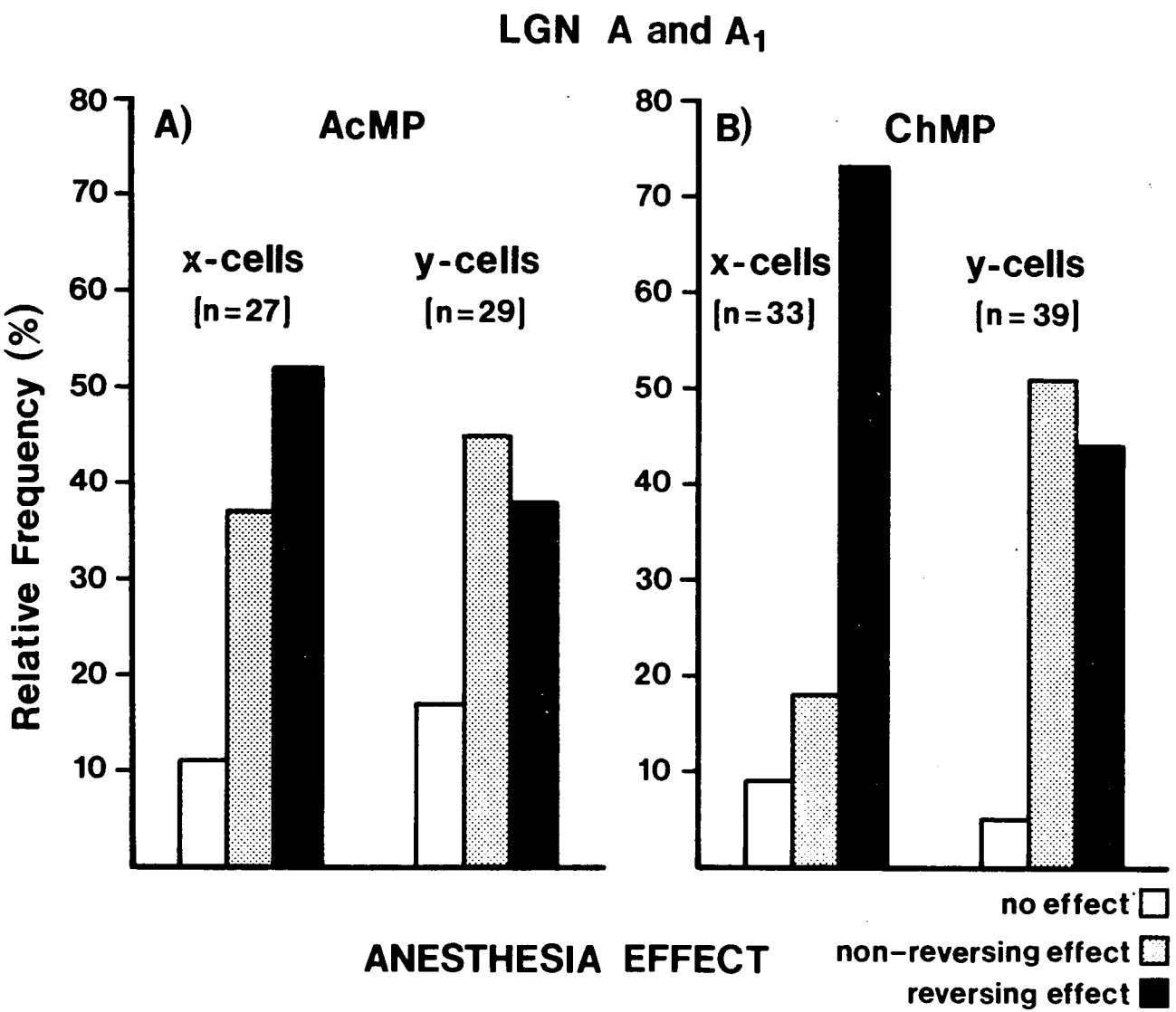
Threshold of Response to Optic Chiasm Stimulation.

The impact of anesthesia upon X- and Y-cell excitability was assessed by measuring the threshold to optic chiasm stimulation, under both anesthetized and unanesthetized conditions, for each cell encountered.

Acute monocular paralysis. Complete measurement of this dependent variable was obtained for 56 cells in acutely paralyzed animals, 27 X-type and 29 Y-type (see Figure 4a). Of the acute X-cells, 3 (11%) showed no anesthesia effect, 10 (37%) showed a nonreversing change, and 14 (52%) showed a reversing, anesthesia-related change in threshold (Figure 4a, left side).

FIGURE 4

Relative frequencies of individual units encountered LGN laminae A and A1 (central 10 degrees) which showed no anesthesia effect upon threshold (white bars), nonreversing threshold change (stippled bars), and reversing threshold change (dark bars). X-cells are represented to the left, and Y-cells are represented to the right. Data in 4a were obtained from acute monocularly paralyzed (AcMP) cats. Figure 4b is organized in an identical fashion, but depicts data obtained from chronic monocularly paralyzed (ChMP) cats. N's refer to the total number of cells encountered which fell into each of these categories.


LGN A and A1
A)
AcMP
x-cells
[n=27]
y-cells
[n=29]
B)
ChMP
x-cells
[n=33]
y-cells
[n=39]
Relative Frequency (%)
80
70
60
50
40
30
20
10
ANESTHESIA EFFECT
no effect
non-reversing effect
reversing effect

In 36% of acute X-cells with a reversing effect, threshold was elevated by anesthesia, and in the remainder of the acute X-cells with reversing effects (64%), threshold was depressed by anesthesia (see Figure 5a, left side).

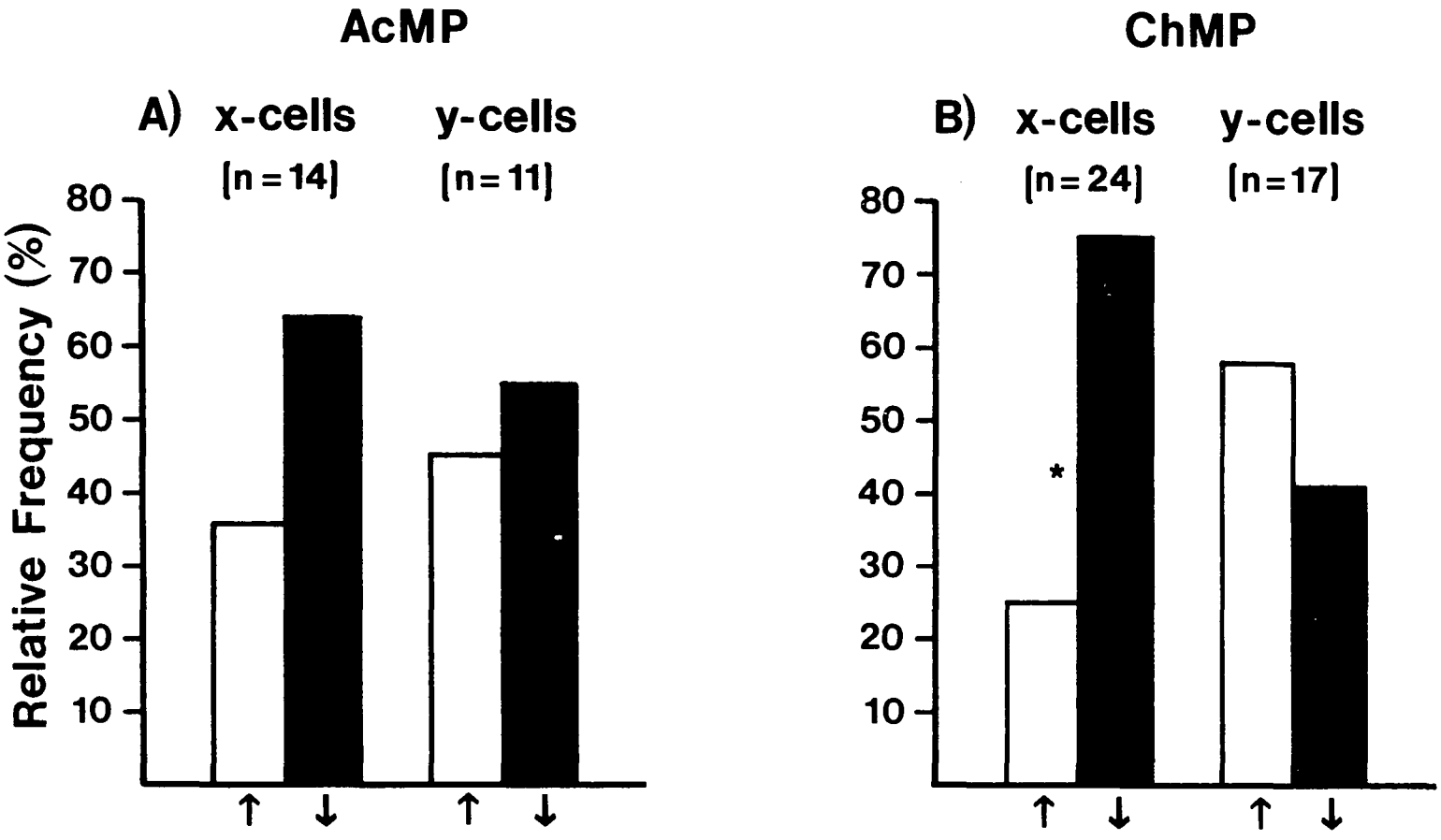
Of the acute Y-cells, 5 (17%) showed no anesthesia effect upon thresholds, 13 (45%) showed nonreversing changes in threshold, and 11 (38%) showed reversing anesthesia-related changes in threshold (Figure 4a, right side). 45% of those with reversing threshold change had threshold elevated by anesthesia, and the remaining 55% had threshold reduced by anesthesia (Figure 5a, right side).

In acute monocular paralysis, therefore, 43% of the cell sample had reversing anesthesia-related changes in threshold, and there may have been a trend towards reduced threshold under anesthesia conditions for both X- and Y-cells. Figure 6a displays the mean of the reversing changes in threshold (from unanesthetized to anesthetized) for both X-cells (left) and Y-cells (right) in acutely paralyzed animals (Figure 6a). There may be a trend towards a differential anesthesia-related threshold change in the two classes, with acute X-cells showing an average reduction in threshold of approximately 3 vsec, and acute Y-cells showing an average elevation of approximately 36 vsec. However, the variability (indicated by standard error bars) is so great that the X- and Y-distributions overlap extensively. Thus, although a large proportion of X- and Y-cells show reversing anesthesia-related threshold changes, these data suggest that a given cell in either class is as likely to increase as to decrease threshold, in response to anesthesia induction.

FIGURE 5

Relative frequencies of individual cells encountered in LGN laminae A and A1 (central 10 degrees) of acute monocularly paralyzed (AcMP) cats (Figure 5a), which showed reversing (reliable) changes in threshold, with anesthesia induction: threshold increases (white bars, up arrows); threshold decreases (dark bars, down arrows). X-cells are represented to the left, and Y-cells to the right. Figure 5b is organized in an identical fashion but depicts data obtained from chronic monocularly paralyzed (ChMP) cats. N's refer to the number of cells in each category that showed reversing changes in threshold. The asterisk in 5b, X-cell column, indicates that the direction of threshold change in ChMP X-cells is statistically significant (sign test, $p<.05$).

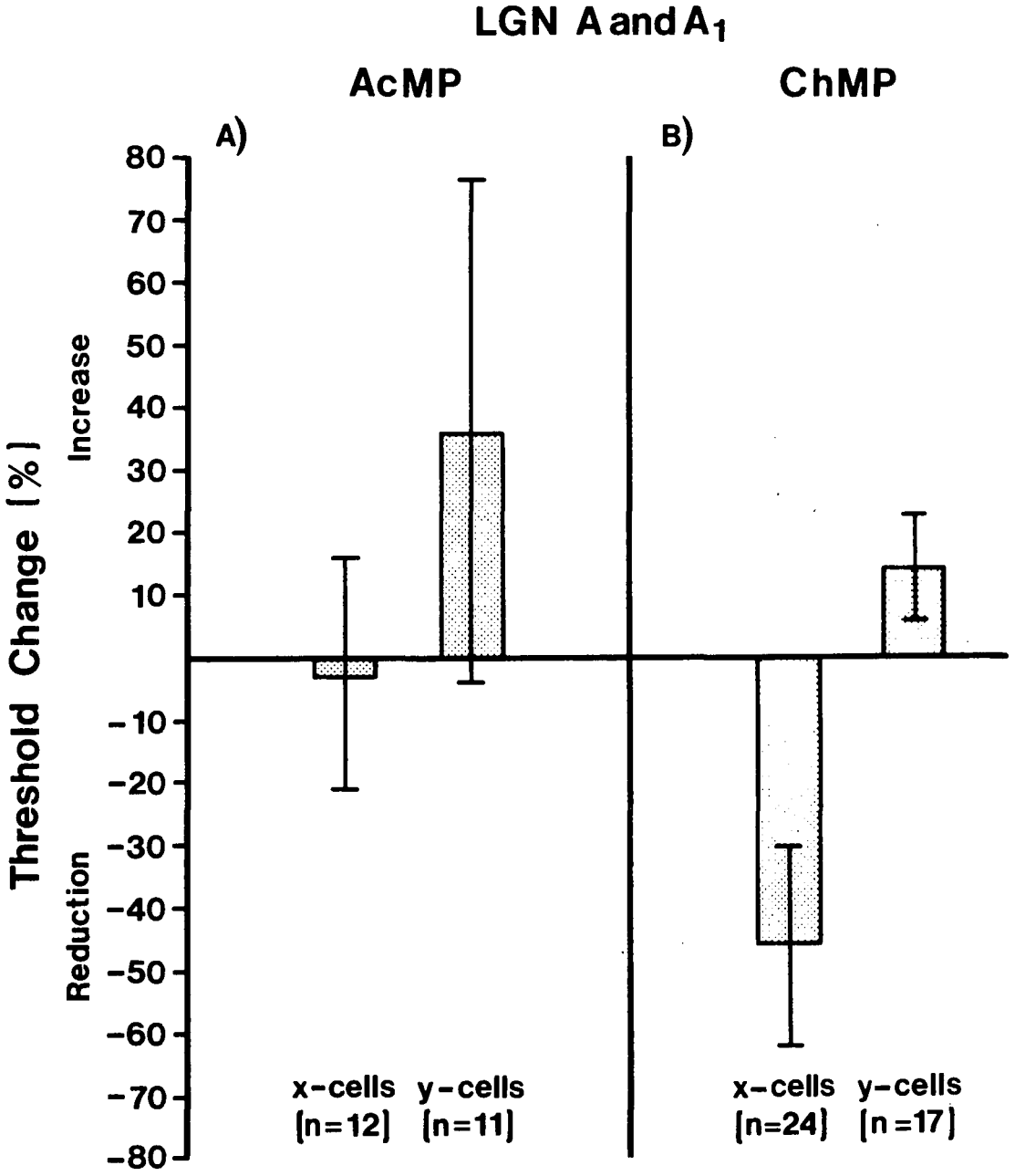
LGN A and A_1



Effect of Anesthesia upon Threshold

FIGURE 6

Mean magnitude of reversing change in threshold, associated with anesthesia induction, for X-cells (left) and Y-cells (right), encountered in LGN laminae A and A1 (central 10 degrees) of monocularly paralyzed cats. The magnitude of change is expressed on the ordinate in terms of percentage of change in threshold from the unanesthetized to the anesthetized condition (threshold unanesthetized - threshold anesthetized/ threshold unanesthetized). Upward deflection represents threshold increase with anesthesia. Downward deflection represents threshold decrease with anesthesia. Figure 6a depicts data obtained from acute monocularly paralyzed (AcMP) cats. Figure 6b is organized in an identical fashion, but depicts data obtained from chronic monocularly paralyzed (ChMP) cats. N's refer to the number of units showing reversing change, in each category.


LGN A and A1
AcMP
ChMP
A)
B)
Threshold Change [%]
Increase
Reduction
80
70
60
50
40
30
20
10
-10
-20
-30
-40
-50
-60
-70
-80
x-cells [n=12]
y-cells [n=11]
x-cells [n=24]
y-cells [n=17]

As one might expect, statistical analyses sensitive to both direction and magnitude of change, over repeated measures, Wilcoxon Matched-pairs Signed-ranks Test (Daniels, 1978), revealed no significant pattern of reversing threshold change for either X- or Y-cells (X-cells threshold/anesthetized with threshold/unanesthetized, Wilcoxon $p>.05$; Y-cells: threshold/anesthetized with threshold/unanesthetized, Wilcoxon $p>.05$). Therefore, while a large percentage of both X- and Y-cells (43%) show reversing threshold changes associated with the induction of anesthesia, the pattern of threshold change is not consistent, and as such, is not suggestive of systematic anesthesia effects in acutely paralyzed animals.

Chronic monocular paralysis. Complete threshold measurements were obtained from 74 cells in chronic monocularly paralyzed animals; 33 X-type and 39 Y-type (see Figure 4b). Of the X-cells, 3 (9%) showed no anesthesia effect, 6 (18%) showed nonreversing changes, and 24 (74%) showed a reversing change in threshold (Figure 4b, left side). 25% of X-cells with reversing changes had thresholds elevated by anesthesia, and the remaining 75% had thresholds lowered by anesthesia (Figure 5b, left side).

Of the chronic Y-cells, 2 (5%) showed no anesthesia effect upon threshold, 20 (51%) showed nonreversing threshold changes, and 17 (44%) showed reversing changes in threshold (Figure 4b, right side). Of the cells with reversing effects, 58.8% showed thresholds elevated by anesthesia, and the remainder (41.2%) showed thresholds lowered by anesthesia (Figure 5b, right side). The mean of the reversing changes in threshold for chronic X-cells (Figure 6b, left) and that for chronic

Y-cells (Figure 6b, right) indicate that in chronic paralysis, average X-cell thresholds decrease approximately 46 vsec with anesthesia induction, and average Y-cell thresholds increase approximately 14 vsec with anesthesia induction. Further, relative to the corresponding observations in acute paralysis (Figure 6a), both X- and Y-cells in chronic paralysis show less variability in direction and magnitude of threshold change with anesthesia (indicated by the standard error bars), forming relatively distinct X- and Y-patterns of threshold change. Therefore, the major point of contrast between the anesthesia-related threshold changes observed in acute animals, and those in chronic animals, is not the proportion of the sample showing reversing change, since in each case a substantial proportion of the sample does show reversing change. Rather, acute and chronic animals differ in terms of consistency in direction and magnitude of the changes. When both direction and magnitude of threshold change were taken into account, changes in both X- and Y-cells reached significance (X-cells, Wilcoxon $p>.05$; Y-cells, Wilcoxon $p>.05$) only in chronic animals. Thus, while in acute animals, anesthesia-related increases and decreases in threshold were equally probable for both X- and Y-cells, in chronic animals, the cells showed distinct X- and Y- patterns of change: X-cells tended to decrease threshold with anesthesia; Y-cells tended to increase threshold with anesthesia.

The observation that X-thresholds are decreased and Y-thresholds are increased by anesthesia induction in chronic but not in acute animals parallels the observation that the encounter rate for X-cells is increased and the encounter rate for Y-cells is decreased by anesthesia

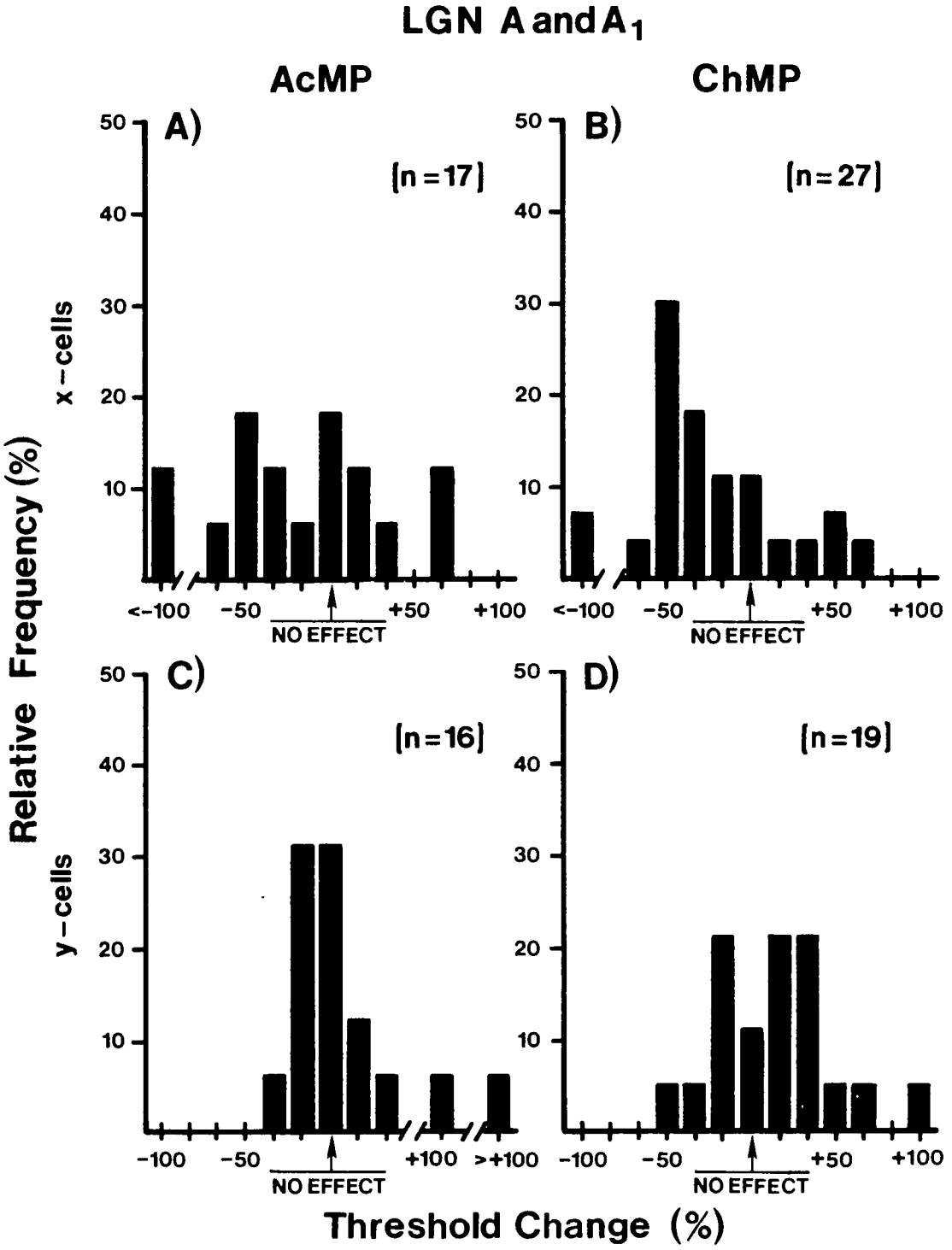
induction in chronic but not in acute animals (Experiments 1 and 2). This parallel between the sensitivity to anesthesia of thresholds in individual cells, and of the X/Y ratio in a population of these cells, suggests that threshold change in individual X- and Y-cells that exceeds some "critical" magnitude, may underlie a change in the probability of encountering cells of each type, thus producing a shift in the X/Y ratio.

The Relationship Between Single Unit Excitability and Population Encounter Rates

As a means of exploring this issue, Figure 7 displays the relative frequency distribution of size of reversing threshold change in response to anesthesia, for individual X- (top) and Y-cells (bottom), in both acute (left side) and chronic (right side) animals. The values on the abscissas represent magnitude of change in threshold (in percentage terms) for individual cells, from the unanesthetized to the anesthetized condition. Cells that show no change in threshold with anesthesia induction are represented at the midpoint of each abscissa (labled - no effect). Cells that show reversing change in one direction or the other are represented at increasing distances from the "no effect" position, according to direction and magnitude of threshold change (in percentage terms). As mentioned previously, none of the cells which showed nonreversing changes in threshold were included in these figures. Five cells showed evidence of complete suppression in one of the anesthesia conditions. These cells are represented at extreme positions on these graphs, and are assigned an arbitrary

FIGURE 7

Relative frequencies of various magnitudes of reversing changes in threshold with anesthesia exhibited by cells encountered in LGN laminae A and A1 of acute (AcMP - a and c, left column) and chronic (ChMP - b and d, right column) monocularly paralyzed cats. X-cell data are represented in the top row (a and b) and Y-cell data are represented in the bottom row (c and d). The values on the abcsissas denote percentage of change in threshold from the unanesthetized to the anesthetized condition (threshold unanesthetized - threshold anesthetized / threshold unanesthetized) The middle value on each abscissa represents no effect, and increasing magnitudes of change are represented at increasing distances to the left and right, indicating threshold decrease and threshold increase respectively. Extreme values in the abscissas (i.e. > 100 % or < 100 %) represent cases in which cells were completely silenced, either by anesthesia induction or by recovery from anesthesia. N's refer to number of cells represented in each graph.


LGN A and A1
AcMP
ChMP
A)
[n=17]
B)
[n=27]
C)
[n=16]
D)
[n=19]
x-cells
y-cells
Relative Frequency (%)
50
40
30
20
10
<-100
-50
+50
+100
NO EFFECT
-100
+100
>+100
Threshold Change (%)

value of greater than (or less than) 100% threshold change. Cells in the last category are included here for the purpose of description, but were excluded from the statistical analyses and from the computations underlying Figure 6, because of the difficulty of assigning an objective value for threshold change. This exclusion was necessary because threshold measurements were unobtainable when the cells were completely unresponsive to stimulation.

Figure 7a displays the frequency distribution of threshold changes, with anesthesia induction, in acute X-cells. Excluding the extreme values (< 100%, far left), the remaining acute X-cell thresholds are distributed rather symmetrically about the "no effect" position (30% increasing threshold, and 42% decreasing threshold with anesthesia induction), although there is a slightly increased frequency in the direction of threshold decrease with anesthesia induction. The two acute X-cells showing evidence of complete reversing suppression are shown at the extreme left of Figure 7a, which indicates that threshold was greatly reduced by anesthesia induction.

The corresponding distribution of values for chronic X-cells is presented in Figure 7b. In contrast to the relative symmetry of the acute X-cell distribution, the chronic distribution of threshold change favors quite heavily the direction of threshold reduction with anesthesia. There are two extreme cases of threshold reduction with anesthesia (cells that were completely suppressed under unanesthetized conditions). Excluding these extreme values (far left), the asymmetry of this distribution is still such that only 19% of chronic X-cells increase threshold in response to anesthesia (Figure 7b, right side),

while 63% of these cells decrease threshold with anesthesia induction.

Examination of Figures 7a and 7b suggests that the various magnitudes of threshold change with anesthesia induction form a continuum. This continuum ranges from no effect to moderate and then to marked effects in both directions (threshold increases and decreases with anesthesia), with 9% of the entire sample exhibiting complete suppression under unanesthetized conditions. The critical contrast, however, between acute and chronic X-cell responses to anesthesia, lies in the observation that only 36% of acute X-cells show anesthesia-related reductions in threshold of between 20% and 100%, whereas 52% of chronic X-cells show reductions of this magnitude. As pointed out previously, the magnitude and direction of threshold changes are statistically significant in chronic X-cells (Wilcoxon $p<.001$), but not in acute X-cells (Wilcoxon $p>.05$).

Figure 7c displays anesthesia-related threshold changes in acute Y-cells. Although there is one case of extreme threshold increase (a cell completely suppressed by anesthesia induction), and another case tending toward this extreme, on the whole, this distribution is symmetrical. Threshold in 37% of these cases decreased with anesthesia, and excluding the extreme value (far right), in 30% of the cases, threshold increased with anesthesia.

The chronic Y-cell distribution of threshold changes (Figure 7d) is asymmetrical. 30% of chronic Y-cells decreased threshold with anesthesia and 60% of the sample increased in threshold with anesthesia induction. The magnitude of the threshold increase with anesthesia induction is statistically significant for chronic Y-cells (Wilcoxon

$p<.020$), but not for acute Y-cells (Wilcoxon $p>.05$).

Thus, Y-cells, like X-cells, demonstrate a continuum of magnitude of threshold change in response to anesthesia. This continuum ranges from no effect, through moderate and extreme effects in each direction, with one cell exhibiting complete suppression under the anesthetized condition. As is true for X-cells, the critical point of contrast between acute and chronic Y-cells is the proportion of the sample showing large magnitude changes in threshold. While only 12% of acute Y-cells show anesthesia-related increases in threshold of between 20% and 100%, 36% of chronic Y-cells show threshold increases in this range.

As stated earlier, the fact that in chronic animals, the threshold of X-cells appears to be lowered by anesthesia, and that of Y-cells appears to be raised by anesthesia is parallel to the observation (from Experiments 1 and 2) that in chronic animals, anesthesia increases the X/Y ratio. However, since obvious shifts from measurable activity levels to silence were observed in only a few cells, and the preponderance of the observed changes were relative increases and decreases in threshold (see Figure 7), the parallel between the impact of anesthesia upon the X/Y ratio and upon unit thresholds can be interpreted to suggest that samping with a microelectrode may be biased against cells that are under a moderate to severe degree of suppression. This explanation implies that a change in sampling technique, to one less dependent upon ongoing activity for detection, would result in a failure to observe any change in the X/Y ratio, related to either duration of monocular paralysis, or manipulation of anesthesia state. In this view, the range of excitability thresholds, exhibited by X- and

Y-cells, contains a critical value for detection: Cells whose thresholds are below this value are isolated and recorded. Cells whose thresholds are above this value, are on the average, not detected. Implicit in this explanation, is the notion that for individual cells, a threshold reduction (anesthesia-related) of sufficient magnitude to cross this boundary, results in detection.

If a systematic pattern of threshold change in individual cells predicts a systematic change in the X/Y ratio (and assuming that once a cell is isolated, recordability is maintained in spite of these threshold changes), there should then be a relationship between the direction and magnitude of threshold change (associated with anesthesia induction) in a sample of cells, and the state of anesthesia under which such cells were encountered. That is, if the encounter rate for a given class of cells is controlled by the relative excitability of cells in that class, the present results suggest that in chronic animals, X-cells characterized as X-type independent of any threshold parameter that show large anesthesia-related decreases in threshold should be encountered more often under anesthetized than under unanesthetized conditions. Conversely, Y-cells (characterized as Y-type independent of any threshold parameter) showing a large anesthesia-related increase in threshold should be encountered more often in unanesthetized than in anesthetized conditions. These predictions are evaluated in the following section.

The Relationship Between Magnitude of Threshold Change for Individual Cells and Anesthesia Condition at Encounter

In order to assess the relationship between magnitude of threshold change in individual cells and anesthesia condition under which these cells are encountered, the data presented in Figure 7 were reorganized according to the anesthesia condition under which the cells were encountered. Figure 8 thus displays the percentage of change in threshold for chronic X-cells (top) and chronic Y-cells (bottom), encountered with the subject unanesthetized (left) or anesthetized (right). Figure 9 presents the corresponding results from acute animals, organized in an identical fashion.

Inspection of Figure 8a reveals that chronic X-cells, encountered with the subject unanesthetized, show an anesthesia-related reduction in threshold approximately twice as often as they show an increase in threshold with anesthesia. This is the same pattern observed in acute X-cells encountered unanesthetized (Figure 9a). Chronic X-cells encountered with the animal anesthetized, however, were nearly five times as likely as chronic X-cells encountered unanesthetized to decrease threshold with anesthesia. This pattern of threshold change with anesthesia was not seen in the corresponding acute paralysis condition (acute X-cells encountered with the animal anesthetized, Figure 9b), which shows a nearly symmetrical distribution of values. Further, when these changes occurred their magnitude tended to be larger. 63% of chronic X-cells, encountered anesthetized, showed a threshold reduction of greater than 20%,

FIGURE 8

Relative frequencies of various magnitudes of reversing change in threshold with anesthesia, exhibited by cells encountered in LGN laminae A and A1 of chronic monocularly paralyzed (ChMP) cats. X-cell data are represented in the top row (a and b), and Y-cell data in the bottom row (c and d). The left column (a and c) depicts data from cells initially encountered with the animal unanesthetized, and the right column (b and d) depicts data from cells initially encountered with the animal anesthetized. The values on the abscissas denote percentage change in threshold from the unanesthetized to the anesthetized conditions (threshold unanesthetized - threshold anesthetized / threshold unanesthetized). The midpoint on each abscissa represents no effect, and increasing magnitudes of threshold change are represented at increasing distances to the left and right, indicating threshold decrease and threshold increase respectively. Extreme values on the abscissas (i.e. < 100 % or > 100 %) represent cases in which cells were completely silenced, either by anesthesia induction, or by recovery from anesthesia. N's refer to total number of cells in each graph.

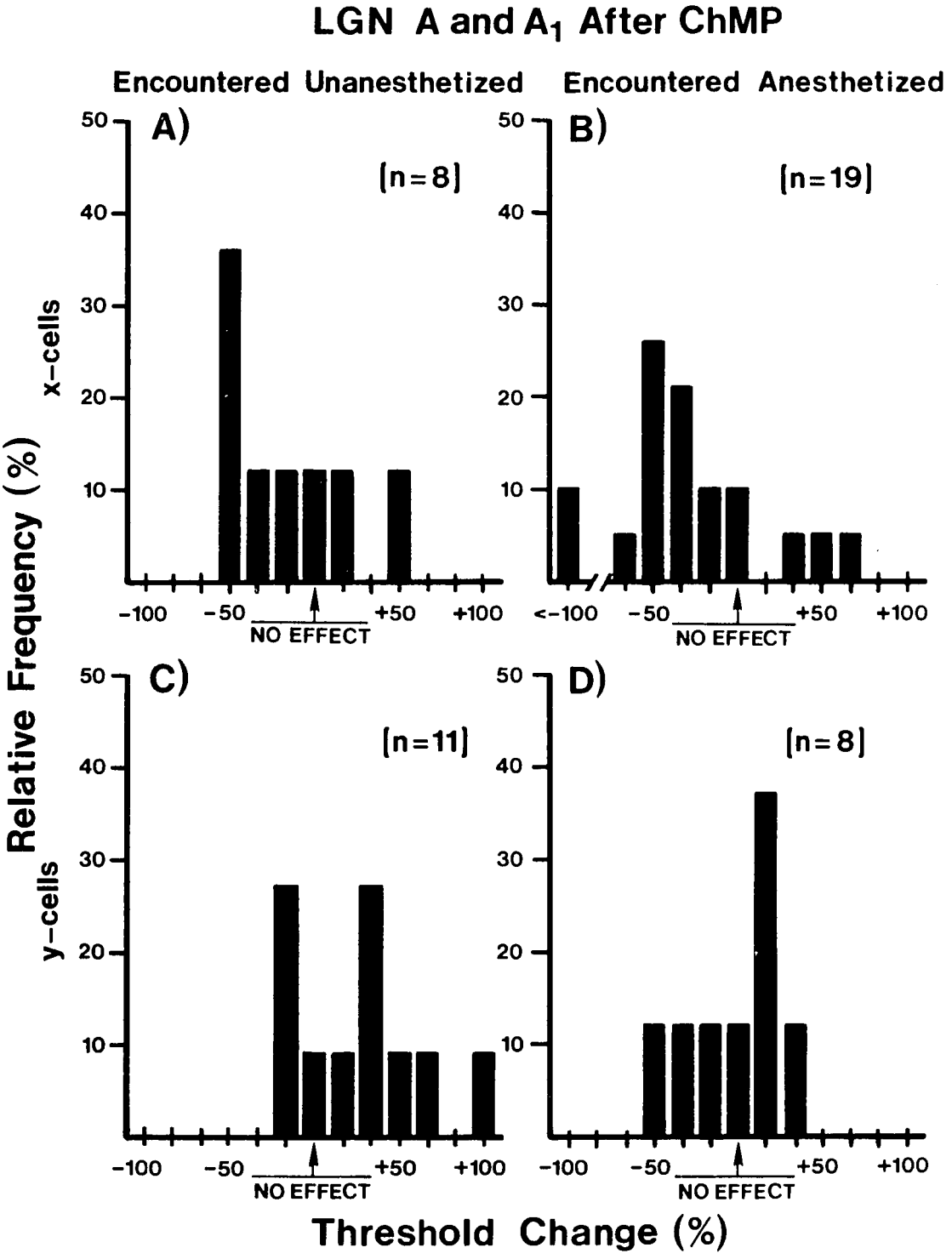
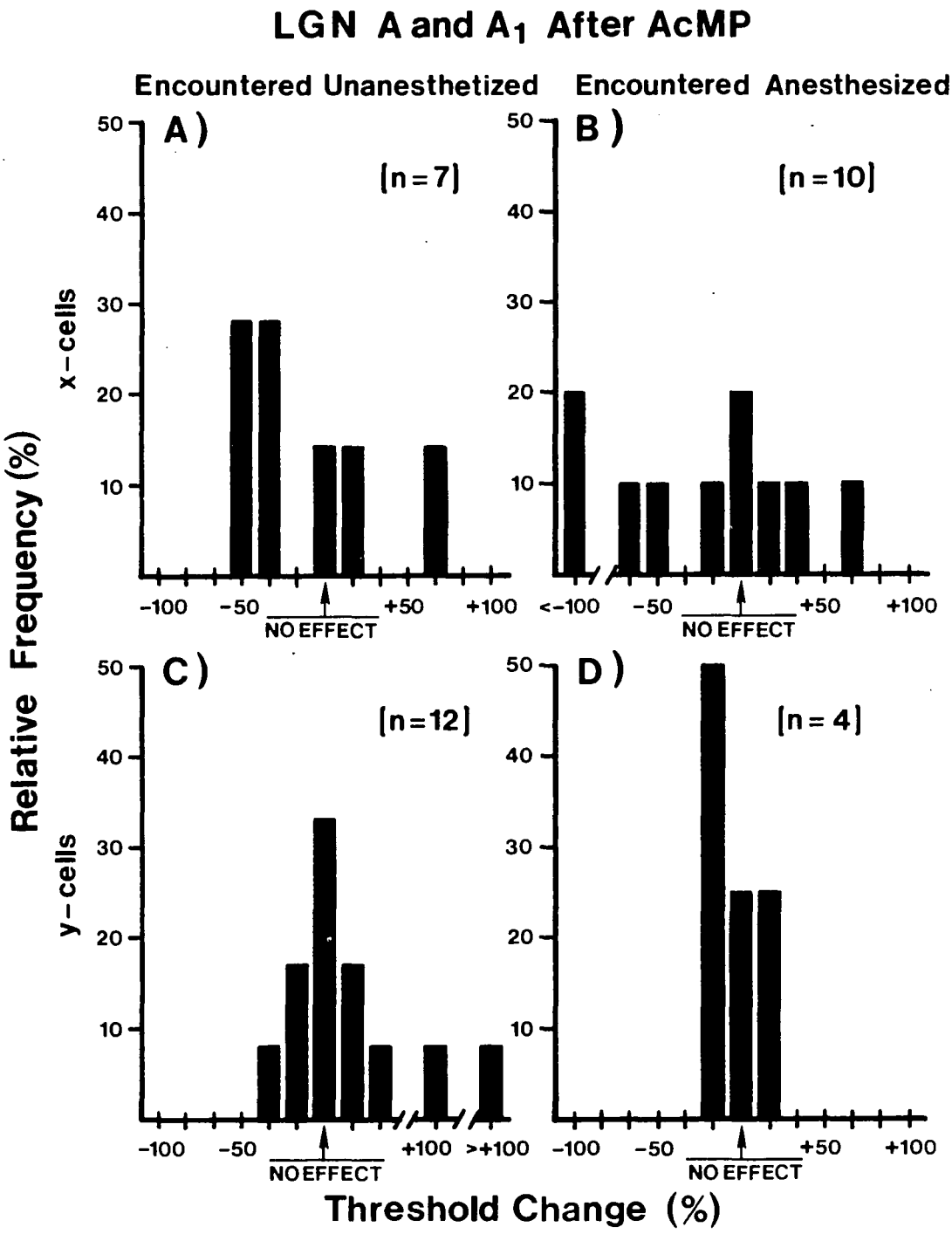

LGN A and A1 After ChMP
Encountered Unanesthetized
Encountered Anesthetized
A)
[n=8]
B)
[n=19]
C)
[n=11]
D)
[n=8]
x-cells
y-cells
Relative Frequency (%)
50
40
30
20
10
-100
-50
+50
+100
<-100
NO EFFECT
Threshold Change (%)

FIGURE 9

Relative frequencies of various magnitudes of reversing change in threshold with anesthesia, exhibited by cells encountered in LGN laminae A and A1 of acute monocularly paralyzed (AcMP) cats. X-cell data are represented in the top row (a and b), and Y-cell data in the bottom row (c and d). The left column (a and c) depicts data from cells initially encountered with the animal unanesthetized, and the right column (b and d) depicts data from cells initially encountered with the animal anesthetized. The values on the abscissas denote percentage change in threshold from the unanesthetized to the anesthetized conditions (threshold unanesthetized - threshold anesthetized / threshold unanesthetized). The midpoint on each abscissa represents no effect, and increasing magnitudes of threshold change are represented at increasing distances to the left and right, indicating threshold decrease and threshold increase respectively. Extreme values on the abscissas (i.e. < 100 % or > 100 %) represent cases in which cells were completely silenced, either by anesthesia induction, or by recovery from anesthesia. N's refer to total number of cells represented in each graph.


LGN A and A1 After AcMP
Encountered Unanesthetized
Encountered Anesthesized
A)
[n=7]
B)
[n=10]
C)
[n=12]
D)
[n=4]
x-cells
y-cells
Relative Frequency (%)
50
40
30
20
10
-100
-50
+50
+100
<-100
>+100
NO EFFECT
Threshold Change (%)

whereas only 49% of chronic X-cells, encountered unanesthetized, showed threshold reductions of this magnitude. The latter proportion is equivalent to that observed in acute X-cells encountered unanesthetized (50%), and to that for acute X-cells encountered anesthetized (52%). Thus, it appears that the greater part of the large magnitude (>20%) reduction in threshold, in chronic X-cells (Figure 7b), occurs in those cells encountered with the subject anesthetized. Statistical analyses support this impression, since anesthesia-related decrease in threshold is statistically significant in chronic X-cells encountered anesthetized (Wilcoxon, $p<.05$), but not in chronic X-cells encountered unanesthetized (Wilcoxon $p>.05$), or in acute X-cells encountered either anesthetized (Wilcoxon $p>.05$) or unanesthetized (Wilcoxon $p=.463$). Although the present methods do not permit identification of the exact threshold value that might be associated with a radical change in recordability, the fact that X-cells showing large reductions in threshold with anesthesia induction are preferentially encountered under anesthetized conditions suggests that such a "critical" value might exist.

This approach, applied to the sample of anesthesia-related threshold changes in chronic Y-cells, also produced results consistent with the notion that relative excitability of cells in a particular class controls the relative encounter rate for cells in that class. That is, while chronic Y-cells which were encountered anesthetized (Figure 8d) showed a weak trend toward a threshold increase with anesthesia, chronic Y-cells encountered with the animal unanesthetized were more than twice as likely as those encountered anesthetized to increase threshold with anesthesia induction. Acute Y-cells encountered

unanesthetized (Figure 9c) had a moderate tendency to show an increase in threshold with anesthesia, and acute Y-cells encountered anesthetized (Figure 9d) showed a decrease in threshold threshold with anesthesia, although in the latter case the sample size is quite small (n=4). Further, 54% of chronic Y-cells encountered unanesthetized showed large threshold increases (between 20% and 100%), relative to 12% of chronic Y-cells encountered anesthetized, to 24% in acute Y-cells encountered unanesthetized, and to 0.0% of acute Y-cells encountered anesthetized. Statistical analyses revealed significant anesthesia-related threshold change in chronic Y-cells encountered unanesthetized (Wilcoxon p=.028), but not in those encountered anesthetized (Wilcoxon p=1.00), or in acute Y-cells encountered either anesthetized (Wilcoxon p=.273) or unanesthetized (Wilcoxon p=.327). It appears therefore, that chronic Y-cells encountered unanesthetized and chronic X-cells encountered anesthetized may account for the bulk of the anesthesia-related threshold change (threshold increase for Y-cells; threshold decrease for X-cells) that is characteristic of these cell types in chronic animals. Although possible distortion of these results by small sample size cannot be ruled out absolutely, the Wilcoxon analysis is routinely used with samples even smaller than these, and does appear capable of analyzing samples as small as these (Daniels, 1978).

Subpopulations of X- and Y-cells?

The fact that chronic X- and Y-cells showing large threshold change with anesthesia were each encountered preferentially in a particular anesthesia condition raises the possibility that each group is a functionally distinct subset of either X- or Y-cell populations.

However, efforts to distinguish these cells, on the basis of their functional properties, from other X- or Y-cells, were largely unsuccessful. One exception is that chronic X-cells showing large reductions in threshold with anesthesia induction were more likely than other chronic X-cells to have afferents with conduction velocities in the lower end of the X-cell range, less than 20 meters/second; 69% of X-cells showing large threshold reductions had relatively low CV's (<20.0 m/sec.), while only 33% of all other X-cells had CV's in this range. Thus, it is possible that X-cells with lower X-type conduction velocities are more likely to show threshold changes of sufficient magnitude to promote a change in the probability of detection.

Possibility of Cumulative Anesthesia Effects

Cells with nonreversing threshold changes comprised a relatively large portion of the total sample of units encountered in Experiment 3 (see Figure 4). The threshold changes shown by these cells were excluded from the analyses (see methods). It is possible however, that the probability of encountering cells of this type was itself systematically affected by the number of anesthesia cycles that a given subject had previously undergone, and that increased encounters for cells with nonreversing changes is related to either deteriorating health, or to some other cumulative anesthesia impact. Implied here is the notion that these cells would have, if freed from this influence, behaved differently, leading to a change in the overall pattern of results.

If repeated cycling of anesthesia state contributed to the present results in this way, more cells with nonreversing changes should have

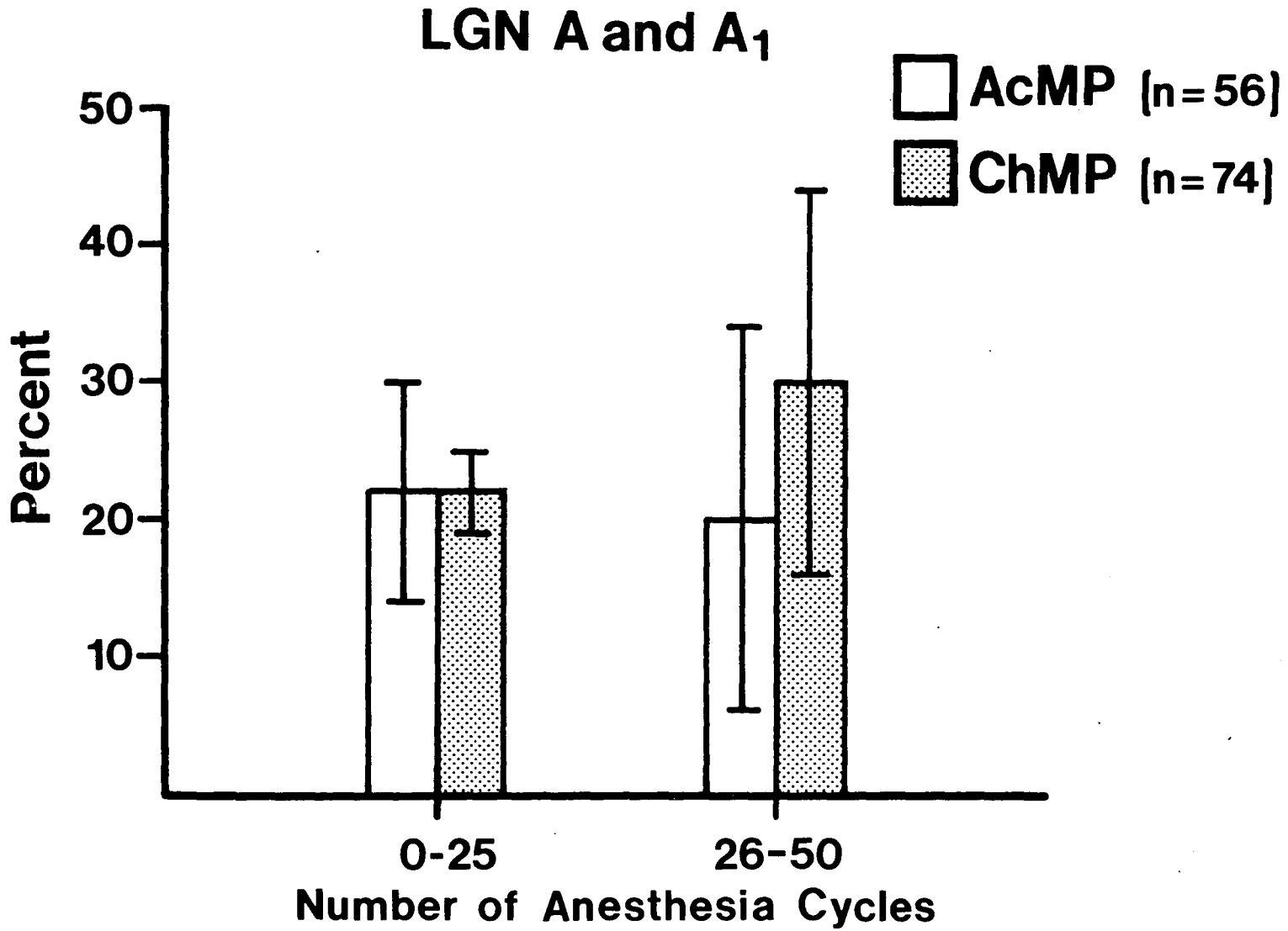
been encountered late in each experiment, after many repeated anesthesia cycles, rather than early in each experiment, after relatively few anesthesia cycles. To assess this possibility, Figure 10 displays the rate of encountering cells with nonreversing threshold changes as a function of the number of anesthesia cycles (for X- and Y-cells combined). Inspection of Figure 10 reveals no change in the encounter rate for such cells, over increasing numbers of anesthesia cycles. Therefore, it appears unlikely that repeated induction of and recovery from anesthesia systematically distorted the present results, by causing the exclusion of data which, if included, would have changed the pattern of results.

Possibility of Electrode Sampling Bias.

A concern raised by Garraghty et al. (1982) is that the anesthesia-related increase in the X/Y ratio may stem from anesthesia-related tissue stabilization rather than from anesthesia-related changes in the excitability of X- and Y-cells. This concern arose from two observations: 1) in the normal animal, X-cells are smaller than Y-cells (e.g., Friedlander et al., 1982), and may therefore be more difficult to isolate and record with microelectrodes; and 2) shrinkage of all LGN cells after chronic paralysis (Garraghty et al., 1982) might exacerbate any bias against the recording of X-cells, leading to a reduction in the X/Y ratio. Stabilization of the brain (associated with reduction of vascular pulsations, etc., see Garraghty et al., 1982), with anesthesia induction, could offset such a bias and return the X/Y ratio to a normal value.

FIGURE 10

Relative frequencies of cells encountered in LGN laminae A and A1 (central 10 degrees) of acute (AcMP - light bars) and chronic (ChMP - dark bars) monocularly paralyzed cats, which showed nonreversing changes in threshold (possibly indicative of physiological instability), with anesthesia. The values on the abscissa denote the number of anesthesia cycles (anesthetized, unanesthetized, then anesthetized, or vice-versa) animals had undergone (grouped as 1-25 and 26-50). Thus, frequency of occurrence of nonreversing change is plotted as a function of number of previous anesthesia cycles. N's refer to the number of cells showing nonreversing change in threshold in each monocular paralysis condition.


LGN A and A1
AcMP (n=56)
ChMP (n=74)
Percent
50
40
30
20
10
0-25
26-50
Number of Anesthesia Cycles

If this concern is well founded, two predictions should be met: 1) passes made with the animal anesthetized should show a higher sampling density (number of cells/pass) than those made with the animal unanesthetized; and 2) of cells encountered with the animal anesthetized, chronic X-cells should be lost from contact when anesthesia is terminated, more often than chronic Y-cells.

To address the first prediction, sampling density was compared between anesthetized and unanesthetized components of pass-pairs taken from chronic animals. In 2/7 (29%) of the cases, sampling density was higher in anesthetized relative to unanesthetized conditions; in 2/7 (29%), sampling density was equal for the two conditions; and in 3/7 (42%), sampling density was actually higher for the unanesthetized than the anesthetized conditions. These observations therefore fail to support the prediction that sampling density should be higher in anesthetized than in unanesthetized conditions.

The second prediction was addressed by examination of the frequency with which X- and Y-cells, encountered under anesthetized conditions, were lost when anesthesia was terminated. Only one case out of the entire chronic X-cell sample (n=33) was found which fulfilled this prediction. No chronic Y-cells, encountered anesthetized, were lost when anesthesia was terminated. Most cells lost between anesthesia phases 1 and 2 (7/8 or 87%) were cells which were encountered unanesthetized, and lost when anesthesia was induced, presumably due to coughing which often accompanied onset of gas flow into the trachea. These cases were distributed with approximately equal frequency across cell type and paralysis conditions.

In sum, neither the sampling density prediction nor the cell loss prediction was supported by these analyses. It appears therefore that anesthesia-related increases in the chronic X/Y ratio does not stem from anesthesia-related stabilization of the recording preparation.

Summary.

The results of Experiment 1 demonstrated that in chronic animals, induction of anesthesia with nitrous oxide produces an increase in the X/Y ratio to a level which is characteristically observed in acute paralysis/unanesthetized. In acute paralysis, induction of nitrous oxide anesthesia had no impact upon the X/Y ratio.

Experiment 2 was an attempt to determine if these results held when tissue variance was drastically reduced and between-subjects variance was completely eliminated. In strict parallel to the results of Experiment 1, the results of Experiment 2 indicated that nitrous oxide anesthesia produces an increase in the X/Y ratio in chronic, but not in acute animals.

In Experiment 3, measurements of the functional properties of X- and Y-cells, under both anesthetized and unanesthetized conditions, indicate no changes in either receptive field properties or the temporal compartments of retinogeniculate conduction that are related to the induction of anesthesia in chronically paralyzed animals. These results mirror the corresponding results obtained from acutely paralyzed subjects. Cell stimulus threshold measurements revealed that in acute animals, while nearly 50% of the X- and Y-cells encountered showed reliable anesthesia-related changes in threshold, in the aggregate, no systematic pattern of threshold increase or decrease emerged in either

class. In remarkable contrast to the acute results (which display a high degree of nonsystematic variability), in chronic paralysis there are systematic patterns of threshold changes in both X- and Y-cells. The magnitude of the anesthesia-related threshold change ranges from barely detectable to infinite (alternating between silence and activity), but the grouped pattern is differential for X- and Y-cells: Chronic X-cells exhibit a reduced threshold under anesthetized (relative to unanesthetized) conditions, and chronic Y-cells show an increased threshold under anesthetized (relative to unanesthetized) conditions.

One group of chronic X-cells was distinguishable from other X-cells in that they tended to have afferents with extremely low conduction velocities, and also tended to show large magnitude reductions in threshold with anesthesia induction. It is possible that these cells represent a functional subpopulation of X-cells which are most affected by chronic paralysis. X-cells in general, however, appeared more labile with respect to axon time and synapse time than Y-cells, particularly in chronic animals. In any case, the tendencies of chronic X-cells to decrease threshold with anesthesia, and of chronic Y-cells to increase threshold with anesthesia, are in parallel to and thus could underlie anesthesia-related increases in X-cell encounter rates and decreases in Y-cell encounter rates.

CHAPTER IV

DISCUSSION

Before discussing the implications of these results for the processes underlying anesthesia effects, the possibility of artifactual contamination of these results will be addressed.

Potential Artifacts Common to all three Experiments.

There are three types of artifacts which could conceivably have influenced the pattern of results found in any of the three experiments. These are 1) order effects, 2) anesthesia effects per se, and 3) anesthesia-related variation in the stability of the recording preparation.

Order Effects. Effects in this category take several forms. First, in each of the experiments, the order in which anesthesia conditions ocurred could have influenced the results. For example, some undetected, residual anesthesia effect upon the X/Y ratio (Experiments 1 and 2), and upon single unit properties (Experiment 3) could have carried over into measurements conducted in a subsequent unanesthetized condition. Further, since Experiments 2 and 3 conducted repeated measurements upon the same tissue (Experiment 2), or upon the same cell (Experiment 3), some form of mechanical damage to the tissue or cell, resulting from prolonged contact with the electrode in one condition, could have influenced the results obtained in a subsequent anesthesia condition. Neither residual anesthesia effects nor mechanical damage

appears likely as a systematic influence, however, since the order of anesthesia conditions was counterbalanced in all three experiments. Thus, approximately one half of the time, the anesthetized condition was the first one, and in the remainder, the unanesthetized condition was first. A second variation on order effects could be referred to as a practice effect. That is, the task of the experimenters, particularly in experiment 3, required a good deal of technical expertise, the capacity for which clearly increases with practice. If, for example, recording of all acute subjects had preceded the recording of chronic subjects, the fact that systematic anesthesia effects were detected in chronic, but not in acute animals, could be attributed to an increase in technical skill, over the course of the experiment. This possibility appears unlikely, however, since acute and chronic subjects were generally interleaved in the data-recording schedule.

Anesthesia Effects per se. This refers to the possibility that anesthesia has a systematic impact upon the X/Y ratio, and upon the characteristics of X- and Y-cells, independent of the duration of monocular paralysis. If this were the case, it would complicate the interpretation of results obtained, using chronic paralysis/anesthetized as a model for acute paralysis. In all three experiments however, sytematic anesthesia effects upon X- and Y-cells were evident in chronic, but not in acute animals (see results). Therefore it appears that a period of exposure to monocular paralysis, or to some equivalent stimulus manipulation with a similarly active physiological impact, must precede a manifestation of systematic anesthesia effects in X- and Y-cells.

Anesthesia-related Variation in Tissue Stability. Anesthesia increased in X/Y ratio in chronic, but not in acute animals (see results, Experiments 1 and 2). It is conceivable that a sampling artifact could have produced this result. In this view, chronic paralysis could have reduced X-cell excitability, which over a period of time, could result in shrinkage of X-cells. Microelectrodes may be biased against isolation and recording of such shrunken cells. Then, anesthesia induction in chronic animals could stabilize the brain against vascular and muscle tension pulsations sufficiently to offset this bias, and return the encounter rate for X-cells to a value characteristic of acute paralysis. An assumption inherent to this explanation is that since Y-cells are larger at the start than X-cells (e.g., see Friedlander et al., 1981), the encounter rate for Y-cells would be less affected by either shrinkage or stabilization. This explanation would predict an increase in sampling density (the number of cells encountered per pass) in chronic paralysis/anesthetized passes relative to chronic paralysis/unanesthetized, since sampling in chronic paralysis/anesthetized would permit access to a larger population of LGN cells. However, this prediction is not supported by the results of the present study since sampling density is unrelated to anesthesia condition (see results). Another prediction of the sampling artifact explanation is that of cells encountered with the animal anesthetized, chronic X-cells should be lost from contact when anesthesia is terminated, more often than chronic Y-cells. This prediction was not supported by the present results since in only one case out of the entire chronic X-cell sample, was the cell lost in the transition from

anesthetized to unanesthetized conditions (see results). Thus, since the sampling artifact explanation makes two clear predictions, and since neither of them holds up under empirical scrutiny, this possibility seems of little concern here.

Potential Artifacts Unique to Experiment 3

There are two possible confounds which appear unique to Experiment 3: cumulative effects of repeated anesthesia induction (as distinct from carry-over effects from trial to trial); and the lack of total certainty that a unit, isolated and observed in the initial anesthesia condition, was the same unit observed in each subsequent condition.

Cumulative Anesthesia Effects. Cumulative anesthesia effects could be either subtle or profound. Profound cumulative effects such as those observed when reveated cycling of anesthesia state induced CNS shock are probably of little concern, since data recording was terminated at the first sign of incipient shock (see method). The notion of a subtle cumulative effect refers to the possibliity that repeated cycling of anesthesia state had a cumulative impact upon the animal's physiology, increasing over the course of the experiment, the probability of encountering cells showing nonreversing changes. Since nonreversing changes were excluded from the analyses, it is possible that such cells, if freed from this influence and thus included in the analyses, would have changed the pattern of results. Such subtle cumulative effects are considered improbable, since over the course of each experiment, no change occurred in the frequency of encountering cells showing nonreversing changes (see results).

Maintained Contact. The second concern, continued contact with and correct identification of a single cell through all anesthesia phases, is somewhat more difficult to satisfy. The approach adopted here was to be rigidly conservative in any case of uncertainty. This conservatism was manifest in two ways (see methods). First, the activity of each cell was continuously monitored, in terms of its "signature" characteristics such as the waveform of its action potential and its pattern of response to electrical and visual stimulation. Consensus amongst all experimenters present was sought in all cases, and lack of consensus resulted in exclusion of the unit from the analyses. Second, given that the unit qualified in the above sense, a change in a given physiological characteristic which occurred between anesthesia phases 1 and 2 was considered reliable only if this characteristic changed again between phases 2 and 3, in the direction of its initial value (i.e. that value observed in phase 1). Unreliable (nonreversing) changes were taken to indicate anesthesia-related lability rather than anesthesia-related change. In addition to demonstrating the reliability of any anesthesia-related change, observation of a reversing change in a unit served to increase confidence that contact with that unit had been maintained throughout the entire series of measurements. That is, there is a low probability of losing one cell and contacting another which is similar to the first, not only in signiture physiological characteristics, but also in its response to change in anesthesia state. Thus, the conservative approach was designed both to minimize misidentification of single units and to maximise the probability that any change in a unit property (related to anesthesia state) was truly

reliable. While the conservative approach does not totally eliminate these concerns, errors which remain should be nonsystematic in their influence, being equally distributed across cell types and paralysis conditions.

The Impact of Nitrous Oxide Anesthesia upon Acute and Chronic X/Y Ratios.

Experiment 1 was an attempt to determine if the impact of nitrous oxide anesthesia upon the X/Y ratio is the same as that of pentobarbital anesthesia (Garraghty et al., 1982). The results of Experiment 1 demonstrated that in chronic monocularly paralyzed animals, nitrous oxide anesthesia promotes an increase in the X/Y ratio that is equivalent to that obtained with pentobarbital anesthesia (see Garraghty et al., 1982). This increase, whether promoted by pentobarbital (as in Garraghty et al., 1982) or nitrous oxide (as in the present study), restores the X/Y ratio to a value equivalent to that observed in acute animals. In acute animals, nitrous oxide anesthesia (present results), like pentobarbital anesthesia (Garraghty et al., 1982), has no impact upon the X/Y ratio. Thus it appears that, in terms of its impact upon both the acute and chronic X/Y ratios, nitrous oxide anesthesia is equivalent to pentobarbital anesthesia.

One problem concerning both the results of Experiment 1 (above) and those of Garraghty et al., (1982), is that collection of data in multiple electrode penetrations and comparison of these to data similarly collected from other animals permits possible contamination of the results with tissue variance and between-subjects variance. Error variance from these sources may have 1) reduced the strength of

anesthesia's impact upon the chronic X/Y ratio and 2) obscured an impact of anesthesia upon the acute X/Y ratio. Experiment 2 therefore replicated Experiment 1, using methods of data collection which eliminate between-subjects variance, and drastically reduce tissue variance (see methods). The results of Experiment 2 showed that in chronic animals, the increase in the X/Y ratio associated with anesthesia induction is sufficiently robust and reliable to be evident in every pass-pair (one pass made with the animal anesthetized, the other, in the same electrode track, with the animal unanesthetized). More importantly, since this data collection technique minimizes tissue variance and eliminates between-subjects variance, and since even with this method, acute animals show no systematic anesthesia effects, it would appear that neither of these sources generated sufficient error variance to obscure any possible anesthesia effects upon the acute X/Y ratio. This conclusion is also supported by results obtained in Experiment 3, since the results of Experiment 3 demonstrated systematic anesthesia effects upon unit properties in chronic but not in acute animals, in spite of the fact that the methods of Experiment 3 totally eliminated between-subjects variance and tissue variance (see results).

Processes in LGN Cells Underlying Anesthesia Effects

Five processes were proposed as possible bases for the impact of anesthesia upon the X/Y ratio in chronic animals: 1) X-suppression; 2) Y-facilitation; 3) combined X-suppression and Y-facilitation; 4) X-response distortion; and 5) Y-afferent unmasking. In this context, the term "process" refers to a change in LGN single unit characteristics, as distinct from change in the activity or nature of

neural circuits whose activity can promote LGN unit changes. These will be discussed in a later section. Experiment 3 explored the five alternative hypotheses. The results yielded no support for the alternate hypotheses concerning excitability changes exclusive to either X- or Y-cells alone (Hypotheses 1 and 2), since systematic excitability changes were found in both cell classes. Experiment 3 also yielded no support for hypotheses concerning partial or total change in the functional identity of X-cells (Hypotheses 4 and 5), since no systematic changes in unit classifications were associated with manipulation of anesthesia state. Rather, this experiment demonstrated that anesthesia induction produces systematic decreases in threshold in chronic X-cells and increases in threshold in chronic Y-cells. These results therefore suggest that in chronic animals, reciprocal shifts in the excitability of X- and Y-cells underlie shifts in the X/Y ratio, associated with anesthesia induction (Hypothesis 3).

Processes in LGN Cells Underlying Monocular Paralysis Effects as distinct from Anesthesia Effects

Since anesthesia induction appears to reverse the impact of chronic paralysis upon X- and Y-cells, the results of Experiment 3 could be interpreted to suggest that anesthesia and monocular paralysis have inverse effects upon the same process. Thus if anesthesia increases the chronic X/Y ratio by systematically increasing excitability in X-cells and decreasing excitability in Y-cells, monocular paralysis could produce a reduction in the X/Y ratio by systematic suppression of excitability in X-cells, and facilitation of excitability in Y-cells.

However, the degree to which these results can directly elucidate the nature of the process underlying the reduction in the X/Y ratio produced by chronic paralysis, depends upon the adequacy of chronic paralysis/anesthetized as a model for acute monocular paralysis.

If the model is adequate, then the X/Y ratio increase associated with anesthesia induction would be achieved by disabling the process through which chronic monocular paralysis initially induced the X/Y ratio reduction (a one-process view). This view holds that anesthesia induction reverses the impact of chronic paralysis, rendering chronic paralysis/anesthetized equivalent to acute paralysis. Thus, since anesthesia promotes facilitation of X-cell activity and concurrent reduction in Y-cell activity, by implication, chronic paralysis would promote a suppression of X-cell activity, concurrent with an enhancement of Y-cell activity (a one-process view). It is also possible, however, that anesthesia engages a process that is totally different from that process triggered by monocular paralysis (a two-process view). For example, anesthesia may simply change the relative encounter rates for X- and Y-cells by a process different from the one involved in chronic paralysis effects (e.g., X-facilitation and Y-suppression with anesthesia induction, and X-response distortion after chronic paralysis). In this case, the use of chronic paralysis/anesthetized as a model for acute paralysis is inappropriate, since the X/Y ratio increase in chronic paralysis/anesthetized merely <u>appears</u> to be a reversal of chronic paralysis effects, when in fact there would be two processes operating.

One- vs Two-process Interpretations.

The results of this study cannot directly confirm or disconfirm either of these possibilities. However, the one-process account presents a number of advantages over the two-process account.

First, the two-process account suggests that chronic paralysis effects upon the X/Y ratio are the result of a process that is different in character from that which underlies anesthesia's impact upon the X/Y ratio. Aside from excitability changes (which form the basis for anesthesia effects), two other processes, X-response distortion and Y-afferent substitution, were suggested as possible bases for the reduction in the X/Y ratio after chronic paralysis. Both of these are logical possibilities, but they are largely contradicted by empirical evidence. That is, either hypothesis assumes a pattern of excitatory interaction between Y-ganglion cells and X-geniculate cells. Such "cross wiring" is completely inconsistent with evidence from physiological (Cleland, Dubin & Levick, 1971; Cleland et al. 1976), and combined physiological/anatomical (Friedlander et al., 1981) studies of retinogeniculate connectivity. The one-process view, in contrast, simply requires that X- and Y-cells be sensitive to the influence of an excitability-altering mechanism which can itself be triggered by chronic paralysis, and can then be disabled by anesthesia induction. Further, the two-process account requires an unwieldy and presently unsupported set of assumptions in order to handle two interlocking aspects of the present results: 1) acute/chronic differences in the variability of anesthesia effects upon X- and Y-cells; and 2) the magnitude of the increase in the X/Y ratio, associated with anesthesia induction,

relative to the magnitude of the decrease in the X/Y ratio after chronic paralysis.

Acute - Chronic Differences. Anesthesia has a systematic impact upon the X/Y ratio and upon unit thresholds in chronic, but not in acute animals. In a one-process view, the variability in the impact of anesthesia state in acute animals upon the X/Y ratio in paired-passes (Experiment 2), and upon unit thresholds on a within-cell basis (Experiment 3), may well represent simple physiological variability or sampling variability. Then in chronic animals, anesthesia-related increases in the X/Y ratio and congruent changes in the excitability of X- and Y-cells would result from anesthesia's capacity for disabling the process through which chronic paralysis initially changed these electrophysiological characteristics of LGN units.

Two-process reasoning would argue that in acute animals, anesthetic modulation of X- and Y-thresholds might occur as it does in chronic animals. In acute animals, however, the systematic character of anesthetic modulation of excitability and of encounter rates could be obscured by variability inherent to some subpopulation of X- and Y-cells, which in the chronic phase of paralysis would have been excluded from the sample by the prior impact of a different process, initiated by monocular paralysis. This account requires the assumption that there are at least two distinct subpopulations of LGN X-cells and two of Y-cells. One subpopulation of each class would be sensitive to the influence of a process initiated by monocular paralysis, and the other subpopulation of each class would be sensitive to the influence of a process triggered by manipulation of anesthesia state. The present

results have raised the possibility that there may be a subpopulation of chronic X-cells that may be particularly sensitive to anesthesia state, in that they show large magnitude reductions in threshold with anesthesia induction. This possible subpopulation consists of chronic X-cells which tend to be encountered with the animal anesthetized, and which are distinguishable from other chronic X-cells by the possession of afferents with extremely low conduction velocities (see results). This observation is perhaps consistent with the above-stated subpopulations assumption (required by the two-process view), since the subpopulation in question could correspond to one (a subpopulation of X-cells distinct in some functional sense, which appear particularly sensitive to anesthesia) whose existence is predicted by this assumption. However, in the present results, no corresponding subpopulation was identifiable in acute paralysis. In fact, there was no subpopulation of acute X-cells distinguishable in any terms from the remainder of the acute X-cell sample, much less one which appeared absent or greately decreased in frequency in chronic paralysis (as predicted by the subpopulations assumption). Moreover, exhaustive analysis of the data obtained from Y-cells provided no evidence for the predicted Y-type subpopulations, in either acute or chronic paralysis. Our identification of the chronic X-type subpopulation showing large magnitude anesthesia effects is at present tentative. The issue of X- and Y-type subpopulations certainly merits further exploration, and perhaps with continued rigorous and quantitative assessment of unit characteristics, subpopulations which fit the assumptions of the two process view might be found. At this point, however, the subpopulation

of chronic X-cells tentatively identified here appears equally consistent with both one-process and two-process interpretations of the present results. Thus the subpopulations assumption (required by the two-process view), while consistent with the present results, is at present without independent empirical support. The one-process view is also consistent with the present results (including the possible X-type subpopulation), but does not require this extra assumption concerning X- and Y-type subpopulations.

Relative magnitudes of changes in the X/Y ratio associated with chronic paralysis and with anesthesia induction. The results of Experiments 1 and 2 suggest that the initial X/Y ratio reduction in chronic paralysis is virtually identical in size to the X/Y ratio increase that attends the induction of anesthesia in chronic animals. If two processes were operating, one reducing X-encounter rates and increasing Y-encounter rates after chronic paralysis, and the other triggered by anesthesia operating in an inverse fashion to the first process and on a different subset of X- and Y-cells, it is difficult to imagine that when both processes are engaged (in chronic paralysis/anesthetized), their effects largely cancel one another. For such an outcome to occur, requires that the two processes be inverse in action, of approximately equal strength, and that the subsets of X- and Y-cells affected by each are of nearly equal size. A one-process account, in contrast, simply treats X- and Y-type subpopulations affected by each manipulation as virtually identical, and implies that any differential impact of chronic paralysis upon the excitability of X- and Y-cells is disabled by anesthesia.

While it is not possible to make a definitive choice between one- and two-process interpretations, the principle of parsimony favors a provisional acceptance of the one-process view. Therefore, the ensuing discussion is built around a one-process interpretation.

What is the Function of a Process which is Reciprocally Affected by Monocular Paralysis and Anesthesia?

Several independent and sometimes parallel observations contribute to the suggestion that this process of differential excitability change in X- and Y-cells, triggered by monocular paralysis and reversed by anesthesia, exists in service of binocular interactions. These observations concern 1) the fact that differential influences upon X- and Y-cells are often associated with the direct action or the disruption of either retinal or nonretinal binocular mechanisms, 2) participation of binocular processes in monocular paralysis effects, 3) the sensitivity of both binocular processes and chronic paralysis effects to change in anesthesia state.

First, in addition to characteristic X/Y differences in visual responsiveness (Hoffmann et al., 1972; Wilson et al., 1976; Hochstein & Shapley, 1976; Kratz et al., 1978; Bullier & Norton, 1979), differential excitability changes in X- and Y-cells are often observed both under the direct action of binocular processes, and when the influence of a binocular mechanism is altered in some way. For example, X- and Y-cells are affected by binocular inhibition putatively generated within the LGN (Sanderson, Darian-Smith & Bishop, 1969; Sanderson, Bishop & Darian-Smith, 1971; Singer, 1970; Suzuki & Takahashi, 1970;

Schmielau & Singer, 1974, 1977; Fukada & Stone, 1976; Singer, 1977). However, binocular inhibitory effects per se appear differential for X- and Y-cells, since of the two types, X-cells seem to be more heavily affected by such inhibition (Suzuki & Takahashi, 1970; Fukada & Stone, 1976; Rodieck & Dreher, 1979). Further, X- and Y-cells are differentially sensitive to stimulation of binocular corticofugal mechanisms (Tsumoto, Creutzfelt, & Legendy, 1978) and to stimulation of binocular mechanisms controlling conjugate eye movements (Tsumoto & Suzuki, 1976). Finally, stimulation of a variety of loci in the reticular formation produces a differential impact upon excitability in X- and Y-cells (Singer & Bedworth, 1973; Foote, Maciewicz & Mordes, 1974; Fukada & Stone, 1976; Singer & Schmielau, 1976). According to Singer (1977), most effects of reticular stimulation upon LGN cells result from incapacitation of intrinsic inhibitory interactions in the LGN, a large proportion of which are of the binocular inhibitory type, initially described by Sanderson et al. (1969). If this conclusion is correct, interference with binocular inhibition, intrinsic to the LGN, may account for a large proportion of the differential effects of reticular stimulation, upon excitability in X- and Y-cells. Thus, excluding X/Y differences in visual responsiveness (see above), differential impacts upon X- and Y-cell excitability may be largely attributable to the direct action or disruption of binocular mechanisms. Whether or not all such differential X/Y effects can be explained in this fashion is an empirical question.

Second, it is clear that the reduction in the X/Y ratio after chronic paralysis, results from the influence of a binocular mechanism,

since this reduction is observed in LGN laminae innervated by both the paralyzed and the normal eyes (Salinger et al., 1977b; 1980a). In view of the fact that activation or disruption of retinally mediated binocular processes, produces differential consequences for X- and Y-cells (see above), the differential sensitivity of excitability in X- and Y-cells, to the distortions in retinally mediated binocular stimuli generated by monocular paralysis, is not unexpected (see Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980). Similarly, in view of the differential sensitivity of X- and Y-cells to conjugate oculomotor activity generated by stimulation of the frontal eye fields (Tsumoto & Suzuki, 1976), the differential response of X- and Y-cells to the asymmetric oculomotor disruptions (nonretinally mediated) associated with monocular paralysis (see Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980) is also predictable.

Third, anesthesia disrupts mechanisms which make normal binocular processes (e.g., binocular fusion and stereoscopic depth perception) possible (see Cohen, 1975; Jampolski, 1978). Therefore, the capacity of anesthesia for reversing the reduction in the X/Y ratio after chronic paralysis, is possibly attributable to anesthesia's impact upon certain of these binocular mechanisms. That is, anesthesia induction disrupts 1) the influence of binocular retinal processes (mediated by binocular corticothalamic neurons) upon the LGN (see Richard, Gioanni, Kitsikis & Buser, 1975), an influence which is differential for X- and Y-cells (Tsumoto et al., 1978); and 2) the influence of nonretinal (extraocular proprioceptive) signals upon LGN (Iain Donaldson, personal communication), an influence which also appears differential for X- and

Y-cells (unpublished observations).

In sum, it appears that mechanisms whose direct action or incapacitation promotes a process of differential excitability change in X- and Y-cells, are quite often (if not always) binocular in character. More importantly, however, the above considerations suggest that the process of reciprocal excitability change in X- and Y-cells, triggered by monocular paralysis and reversed by anesthesia, is one which is normally concerned with binocular interactions. The next section, therefore, examines the role of the LGN in binocular processes.

LGN as a Binocular Organ.

As stated earlier, both X- and Y-cells are affected by binocular inhibition (Sanderson et al., 1969, 1971; Suzuki & Takahashi, 1970; Schmielau & Singer, 1974, 1977; Fukada & Stone, 1976; Singer, 1977, Rodieck & Dreher, 1979). However, the binocular sensitivity of LGN units observed in these studies is weak, both in terms of frequency (e.g., approximately 47% of LGN units show binocular inhibition in Suzuki & Takahashi, 1970) and amplitude (binocular inhibition is referred to as "weak", requiring averaging techniques for its detection in Fukada & Stone, 1976). Such a low degree of binocular sensitivity predicts a less marked response to disruptions in binocular interactions than that observed after chronic paralysis. For example, in terms of frequency, approximately 65% of the units in the present study showed reliable modulation of excitability by anesthesia, which presumably results from anesthetic incapacitation of binocular processes (see Jampolski, 1978). These excitability changes were of sufficient magnitude to be observed without computer enhancement, and to produce

significant shifts in the encounter rates for X- and Y-cells (see present results). The present results and those of Garraghty et al. (1982) suggest that differences between the degree of binocularity observed in LGN units in the earlier studies and that observed in studies involving monocular paralysis may stem from two sources: 1) chronic paralysis alters the degree to which LGN units are affected by binocular processes (Garraghty et al., 1982); and 2) in the earlier studies, animals were recorded anesthetized, while in the present study and in Garraghty et al. (1982), animals were recorded unanesthetized (except when anesthesia state itself was an independent variable). Thus, since anesthesia disrupts binocular interactions (Jampolski, 1978), these early reports based upon anesthetized preparations probably underestimated the frequency and intensity of binocular interaction in the LGN. These considerations suggest that the LGN may have a greater role in binocular processes than was previously suspected.

Two visual capacities which depend upon binocular interactions are stereoscopic depth perception and binocular fusion. Each of these would seem to require binocular integration of information regarding both retinal disparity and relative eye position. The fact that LGN units respond to retinal stimuli (for a review, see Lennie, 1980), and to nonretinal proprioceptive stimuli (Donaldson & Dixon, 1980), and are sensitive to disruptions in both classes of stimuli (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980), suggests that the LGN may be a critical component in mechanisms underlying such binocular processes. If this is the case, then brain circuits should be present to promote LGN unit sensitivity to changes in the patterns of binocular

retinal and nonretinal stimulation. In the face of the present (and earlier) results obtained with monocular paralysis, such circuitry must have at least three attributes: 1) functional access to the retinal and nonretinal stimulus distortions associated with monocular paralysis; 2) capability of promoting a differential impact upon X- and Y-cells; and 3) sensitivity to anesthesia state. In the following two sections, therefore, is a review of neural circuits which, on the basis of their functional properties and anatomy, could mediate the impact of chronic paralysis upon X- and Y-cells. Subsequent to these, are sections concerning points at which the outputs of these circuits could be combined and integrated, and points at which these mechanisms may be sensitive to the influence of anesthesia.

1) Circuitry mediating the effects of binocular nonretinal stimulus distortions. One type of stimulus disruption, shown to be critical to the impact of chronic paralysis upon the X/Y ratio, is disruption of nonretinally mediated binocular stimuli, such as extraocular proprioception (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980). Stimuli relating to this type of perturbation are believed to travel centrally via Cranial Nerve V (Alvarado-Mallart, Batini, Buisseret-Delmas & Corvisier, 1975; Batini, Buisseret, & Buisseret-Delmas, 1975), to terminate either in mesencephalic nucleus of Nerve V (Fillenz, 1955; Alvarado-Mallart et al., 1975; Batini et al., 1975), or in the spinal reticular nucleus (Porter & Spencer, 1982), both of which are intrinsic to the reticular formation. Strictly speaking, the passage of extraocular proprioceptive stimuli, through the reticular formation and then directly to the LGN, has not been empirically

demonstrated. However, the presence of such a pathway does appear likely, since 1) extraocular proprioceptive stimuli are conveyed to the reticular formation (Fillenz, 1955; Alvarado-Mallart et al., 1975; Batini et al., 1975; Abrams & Anastee, 1977; Porter & Spencer, 1982), and may be processed there, like somatic proprioceptive signals, which are "gated" or "modulated" in passage through the reticular formation (e.g., see French et al., 1953); and 2) extraocular proprioceptive signals do impact upon unit activity, both in cortex, area 17 (Buisseret & Maffei, 1977; Donaldson, 1979), and area 7a (Anderson & Essick, 1984), and in the LGN (Donaldson & Dixon, 1980). Since the reticular formation contains the initial central target of such stimuli, the mesencephalic nucleus of Nerve V (Fillenz, 1955; Alvarado-Mallart et al., 1975; Batini et al., 1975; Abrams & Anastee, 1977), it is therefore likely that the reticular formation is involved in the mediation of the impact upon the LGN, of any distortion in binocular patterns of proprioceptive stimulation. It is also clear that activity in nearly any part of the reticular formation can influence LGN cells, given the extensive pattern of projections from the reticular formation to the LGN (Bowsher, 1970; Gilbert & Kelly, 1975; Leger, Sakai, Salvert, Touret & Jouvet, 1975; Mcbride & Sutton, 1976). Such reticulothalamic influences are believed to be polysynaptically mediated (Singer, 1973), projecting through several "non-specific" thalamic nuclei (Scheibel & Scheibel, 1958, 1966a, 1966b, 1967; Mancia, Broggi & Margnelli, 1971; Schlag & Wazak, 1970; Yingling & Skinner, 1975). One of these thalamic nuclei in particular, the nucleus reticularis thalami, may function as an interface between the reticular formation and the LGN

(Mukhametov, Rizzolati & Tradardi, 1970; Schlag & Wazak, 1970; Lamarre, Filion & Cordeau, 1971; Yingling & Skinner, 1975). Further, stimulation of various loci in the reticular formation has been shown to produce a differential impact upon the excitability of LGN X- and Y-cells (e.g. Fukada & Stone, 1976; Foote et al., 1977). There thus appears to be at least one brain pathway through which signals concerning disruptions in binocular nonretinal stimulation can impact upon X- and Y-cells.

2) Circuitry mediating the effects of binocular retinal stimulus distortions. Another type of sensory disruption, which is critical to the reduction in the X/Y ratio, associated with chronic monocular paralysis, is distortion of retinally mediated stimuli (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980). Such stimuli are presumably binocular cues which provide the visual system with retinal disparity information (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980). Retinal signals from each eye are carried by both X- and Y-ganglion cells to the LGN, from which they are relayed by X- and Y-LGN cells to visual cortex (for recent reviews, see Rodieck, 1979; Stone et al., 1979; Lennie, 1980; Sherman & Spear, 1982). In terms of excitatory interaction between inputs from each eye, binocularity is first evident at the level of visual cortex, although in inhibitory terms, binocular interaction occurs even at the level of LGN cells (Sanderson et al., 1969, 1971; Singer, 1970; Singer & Bedworth, 1973; Schmielau & Singer, 1974; Fukada & Stone, 1976; Singer & Schmielau, 1976; Schmielau & Singer, 1977; Rodieck & Dreher, 1979). Although reports of reduced binocularity in cortical units after monocular

paralysis (Fiorentini & Maffei, 1974; Maffei & Fiorentini, 1976) could imply cortical integration of signals regarding distortion of retinally mediated stimuli after monocular paralysis, transmission of the results of such a process to LGN X- and Y-cells has not been demonstrated. Visual cortex does however project extensively to the LGN (Szentagothai, Hamori & Tombol, 1966; Guillery, 1967; Hollander, 1970, 1972; Szentagothai, 1973; Kawamura, Sprague & Nimi, 1974; Gilbert & Kelly, 1975; Updyke, 1975). Further, the fact that many (if not most) of the corticogeniculate neurons are binocular (Singer, Tretter & Cynader, 1976; Schmielau & Singer, 1977 Singer, 1977; Tsumoto et al., 1978) supports the view (e.g., see Pettigrew, 1972; Singer, 1977; Burke & Cole, 1978) that corticogeniculate projections have an important role in stereoscopic vision. Finally, stimulation of binocular corticothalamic neurons has a differential effect upon X- and Y-cells (Tsumoto et al., 1978). There thus appears to be a reciprocal loop between LGN and cortex, which has access to information concerning disruptions in retinally mediated patterns of binocular stimulation, and which has the capacity to promote differential impact upon X- and Y-cells. The geniculocortical loop, however, is not the only circuit which could promote a differential effect upon X- and Y-cells, in response to distortion in binocular retinal stimuli, after monocular paralysis. There are in fact other circuits which could perform this function, for example, those circuits underlying intrinsic binocular inhibition in the LGN, of the type initially described by Sanderson et al., (1969). These circuits combine inputs from each eye at the level of the LGN, and prior to the first cortical synapse (Sanderson et al., 1969, 1971; and

others, see above), and thus should be sensitive to distortion in the pattern of binocular retinal stimulation after monocular paralysis. Further, the impact of this type of binocular interaction appears differential for X- and Y-cells (Suzuki & Takahashi, 1970; Fukada & Stone, 1976; Rodieck & Dreher, 1979). Finally, monocular paralysis appears to alter the degree to which X- and Y-cells are affected by binocular inhibition (Garraghty et al., 1982). In summary there appear to be at least two sets of circuits which could mediate the effects upon X- and Y-cells of distortions in binocular retinal stimuli after monocular paralysis. One set involves both the LGN and cortex, and the other involves the LGN alone. The present results do not permit a choice among these alternative circuits. However, for the purposes of the present discussion, it is sufficient to demonstrate that there is at least one pathway which is sensitive to distortions in the pattern of binocular retinal stimulation, and which can produce differential effects upon X- and Y-cells.

3) Integration of retinal and nonretinal binocular stimulus distortions. It is not clear how the output of the system which processes binocular cues relating to distortion of retinally mediated stimuli, interacts with the output of the system (described previously) that could process binocular nonretinal stimulus distortions after monocular paralysis. However, it is clear that integration of retinal and nonretinal signals must occur at some point, since the impact of chronic paralysis upon X- and Y-cells represents the net effect of distortions in both classes of stimuli (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980). Thus the question becomes:

"Where does the integration of the retinal and nonretinal binocular stimuli, generated by monocular paralysis, take place?" Three possibilities will be addressed here. 1) Integration of these cues takes place in LGN units themselves; 2) integration takes place prior to impact upon the LGN cell; and 3) integration takes place at several levels, perhaps simultaneously. The discussion of these alternatives will concern interaction between specific outputs of the reticular formation (relating to nonretinal cues), and of the geniculostriate system (relating to retinal cues), as opposed to the well documented, tonic, nonspecific regulatory influence of the reticular formation upon visual cortex (Moruzzi & Magoun, 1949; French et al., 1953; Moruzzi, 1964; Munsen & Graham, 1971; Munsen & Schwartz, 1972; Orban, Vandebussche & Callens, 1972; Rapisardi, Wilson & Alvarez, 1974, Singer et al., 1976), and upon the LGN (Eisman, Hansen & Burke, 1967; Cohen & Feldman, 1968; Cohen, Feldman & Diamond, 1969; Malcolm, Bruce & Burke, 1970; Munsen & Schwartz, 1972; Burke & Cole, 1978).

The first possibility is that nonretinally mediated stimulus distortions are processed by the pathway involving the reticular formation and retinally mediated stimulus distortions are processed by the pathway involving visual cortex, but the output of these systems is not combined and integrated until the point of contact with an LGN unit. This possibility is supported by the fact that after binocular enucleation (Nakai & Domino, 1968) and after enucleation combined with bilateral ablation of visual cortex (Satinski, 1968), the reticular formation retains some capacity to impact upon LGN cell excitability. More recent experiments indicate that cortical cooling (a reversable

form of inactivation) does not abolish reticular influences upon LGN cells (Schmielau & Singer, 1974, 1977). Further support for relative independence in the processing of retinal distortions by visual cortex, and of nonretinal distortions by the reticular pathway, derives from the conclusion that cortical and reticular influences upon the LGN are mediated by two distinct types of interneurons (Singer, 1977). That is, on one hand, cortical integration of retinal distortions may impact upon LGN cells by inhibiting interneurons intrinsic to the LGN, which among other things, subserve inhibitory binocular interactions between X- and Y-cells (Singer & Bedworth, 1973; Cleland & Dubin, 1977; Dubin & Cleland, 1977; Lindstrom, 1982; but see Friedlander et al., 1981). Reticular integration of nonretinal stimulus distortions, on the other hand, appears to influence LGN cells through inhibition of extrinsic interneurons, whose cell bodies lie in the perigeniculate nucleus (Cleland & Dubin, 1977; Dubin & Cleland, 1977), a structure considered to be part of the reticular nucleus of the thalamus (Scheibel & Scheibel, 1966a, 1966b, 1967; Jones, 1975). In this view, interaction between the nonretinal mechanism (reticular formation to extrinsic, perigeniculate interneurons to LGN) and the retinal mechanism (cortex to intrinsic interneurons to LGN cells) would not occur before the point at which their net effects are felt by individual LGN cells.

In support of the second possibility, three related observations argue for integration of the outputs of retinal and nonretinal mechanisms prior to contact with the LGN unit. First, visual cortical cells with corticothalamic axons (an output link in the retinal mechanism) show particularly strong effects of reticular stimulation,

relative to other visual cortical neurons (Singer et al., 1976). These effects are a result of direct reticulo-cortical modulation, rather than a passive consequence of reticular influences upon signal transmission through the LGN (Singer et al., 1976). Second, proprioceptive signals, generated by mechanical stimulation of one eye, are relayed through the reticular formation (mesencephalic nucleus of nerve V, Batini et al., 1975; or spinal reticular nucleus, Porter & Spencer, 1982), and then to cortex (Buisseret & Maffei, 1977; Donaldson, 1979), which also receives cues relating to retinally mediated stimulus distortions after monocular paralysis (see above discussion of this topic). Finally, cortico-thalamic axons (presumably a late component in the circuit mediating cortical modulation of LGN function), while eventually terminating upon LGN intrinsic interneurons, also send collaterals into the perigeniculate nucleus, thus impacting also upon the extrinsic interneurons (Scheibel & Scheibel, 1966a; Updike, 1975). These extrinsic interneurons are the final component in the proposed pathway mediating reticular influences upon the LGN (see above).

Support for the third possibility, that integration of cues concerning retinal and nonretinal stimulus distortions takes place at several locations, derives from two observations: 1) extraocular proprioceptive stimuli influence LGN unit activity as well as cortical unit activity (Donaldson & Dixon, 1980); and 2) the latency ranges of LGN and cortical responses to extraocular proprioceptive stimulation overlap almost totally (Donaldson & Dixon, 1980). This degree of temporal overlap suggests that extraocular proprioceptive signals are conveyed to cortex and to LGN in parallel. Such a parallel projection

in turn is consistent with the view that integration of retinal and nonretinal signals, stemming from monocular paralysis, may occur in both cortex and LGN.

On the basis of these observations, it appears unlikely that the mechanisms which differentially modulate the excitability of LGN X- and Y-cells in response to distortion of retinal binocular signals, and to distortion of nonretinal binocular signals, maintain complete anatomical segregation until the point at which each influences LGN cell excitability. Rather, it appears that interaction between these mechanisms and integration of their outputs occurs at earlier points such as perigeniculate nucleus and visual cortex, which are up to several synapses removed from the LGN target cell. Further, since proprioceptive signals appear able to influence LGN cells without being relayed through cortex (Donaldson & Dixon, 1980), integration of retinal and nonretinal signals may take place at several levels in the ascending visual pathways (e.g., LGN and cortex), perhaps even concurrently.

Since the reduction in the X/Y ratio after chronic paralysis is reversed by anesthesia induction, both retinal and nonretinal mechanisms, or the integrated output of these mechanisms, must be sensitive to anesthesia state. In the following section, therefore, is a discussion of a number of loci at which anesthesia could impact upon these mechanisms.

4) Basis for anesthesia's impact upon retinal and nonretinal binocular mechanisms. Anesthetic agents like pentobarbital and nitrous oxide, when applied systemically, will impact at any brain locus containing neurons sensitive to the agent. However, brain regions do

differ in their sensitivity to anesthetic agents for a variety of reasons related to metabolic demands and degree of vascularization (French et al., 1953, Darbinjar et al., 1971; Goth, 1981), and to availability of binding sites specific to the agent (Cooper, Bloom & Roth, 1978; Goth, 1981). In this section, two major possibilities will be addressed: 1) Anesthesia, through its impact upon the reticular formation, promotes a nonspecific impact upon the neural processing of all signals, including those relating to monocular paralysis; and 2) Anesthesia's impact is specific and local, targeting processing/integration of signals relating to monocular paralysis, at particular locations such as the reticular formation, cortex, and LGN.

Concerning the first possibility, nonspecific effects, the behavioral manifestations of anesthesia (induced with either sodium pentobarbital or nitrous oxide) are believed to arise from the impact of anesthetic agents upon reticular formation activity (French et al., 1953; Goodman & Mann, 1967; Richards, 1972; Darbinjar et al., 1971; Syka, Popelar & Radil-Weiss, 1975; Goth, 1981). Therefore, one explanation of anesthesia effects in the context of chronic monocular paralysis is that the influence of anesthetic agents upon the reticular formation indirectly impacts upon processing of retinal and/or nonretinal stimuli, critical to the effects of chronic paralysis upon X- and Y-cells. In this view, anesthesia would 1) affect the gating through this network (and to the LGN) of binocular nonretinal signals that are critical to the impact of chronic paralysis upon the X/Y ratio [proprioceptive influences upon LGN units are disabled by anesthesia induction (Iain Donaldson, personal communication)]; and 2) through the

modulatory influence of the reticular formation upon visual cortex, and upon LGN, disrupt integration of binocular retinal stimuli, equally critical to the impact of chronic paralysis upon the X/Y ratio.

The second possibility above is that anesthesia promotes a specific, local impact at one or more points in the circuits mediating chronic paralysis effects upon X- and Y-cells. The previous discussion of retinal and nonretinal circuits suggests three locations at which, either in isolation or conjunction, anesthetic incapacitation of circuits mediating chronic paralysis effects could occur - reticular formation, LGN, and cortex. In the case of pentobarbital anesthesia, a specific, local effect in the reticular formation in the LGN or in visual cortex is conceivable, since each of these structures contains pentobarbital-sensitive neurons. As noted above, reticular processing of signals concerning nonretinal stimulus distortions may be vulnerable to pentobarbital anesthesia, since the reticular formation contains pentobarbital-sensitive neurons (Syka et al., 1975), and since the pathway which carries this type of information is intrinsic to the reticular formation (Alvarado-Mallart et al., 1975; Batini et al., 1975). Further, since anesthesia induction affects reticular gating of somatic proprioception (French et al., 1953), it could produce an equivalent impact upon reticular gating of ocular proprioceptive stimuli. In the LGN, the activity of intrinsic interneurons is facilitated by pentobarbital (Burke & Cole, 1978). These interneurons are believed to contribute to binocular inhibition by reducing the excitability of LGN X- and Y-cells under certain conditions (Cleland & Dubin, 1977; Dubin & Cleland, 1977; Singer, 1977; Burke & Cole, 1978;

Lindstrom, 1982; but see Friedlander et al., 1982). In visual cortex, as in the LGN, pentobarbital could facilitate the action of interneurons, whose putative function in this case is promotion of cortical inhibition (Krnjevic, Randic, & Straughn, 1966), which is believed to underlie binocular integration (reviewed by Hendrickson, 1984). If pentobarbital facilitation of cortical binocular mechanisms resulted in increased stimulation of corticothalamic neurons, an increase in the X/Y ratio might result, since the corticothalamic neurons appear to facilitate selectively X-cell activity (Tsumoto et al., 1978). However, according to some researchers (e.g. see Richard et al. 1975), pentobarbital disables the corticothalamic projection.

These considerations might appear to argue against a local impact of anesthesia in LGN and in cortex. However, it is also logically possible that local saturation of pentobarbital-sensitive neurons in LGN and in cortex could render interneuronal mechanisms in these structures incapable of mediating systematic influences such as selective suppression of a particular cell type. That is, anesthesia could disable interneuronal mechanisms mediating the impact of chronic paralysis, either by silencing inputs to these interneurons, or by increasing their postsynaptic effects to a level at which signal processing is effectively "masked" or otherwise obscured. In either case, the ability of the system to maintain the differential impact of chronic paralysis upon X- and Y-cells, could be lost.

The precise cellular pharmacology of nitrous oxide anesthesia has not been established. While no evidence has yet been presented that is consistent with a direct impact upon the LGN or visual cortex (at a

sublethal anesthetic concentration) in the present context, such local effects are logical possibilities. It is also possible that the change in the X/Y ratio, and the congruent changes in X- and Y-thresholds associated with nitrous oxide anesthesia (present results), like the electrophysiological changes in LGN and cortex, which accompany recruiting responses and PGO waves (Laurent & Guerrero, 1975), are secondary to changes occuring in the reticular formation (French et al., 1953; Goth, 1981).

The present results cannot confirm or disconfirm possibilities of local or central impact, for either pentobarbital or nitrous oxide. However, in a one-process view (i.e. anesthesia disables the mechanism promoting chronic paralysis effects), anesthetic incapacitation of the impact of chronic paralysis could occur at a variety of points in the neural circuitry which transmits the effects of the stimulus distortions, generated by monocular paralysis, to the LGN. The critical locus for anesthesia effects upon X- and Y-cells may be the reticular formation. If this is the case, then the impact of anesthetics in this structure, in addition to inducing behavioral anesthesia, may also lead directly to a disruption in (perhaps even silencing of) binocular nonretinal signals, and indirectly to disruption of cortical or thalamic processing of binocular retinal signals. Both types of signals are necessary for the maintenance of the differential impact of chronic paralysis upon X- and Y-cells (Salinger et al., 1977b; Salinger, Garraghty, & Schwartz, 1980). However, even if the circuits mediating the impact of chronic paralysis upon the X/Y ratio, are not disabled by anesthesia mechanisms, until the point at which they finally converge

upon individual LGN cells, a one-process account would still remain viable.

Alterations in Binocular Function Induced by Monocular Paralysis.

To the extent that a one-process view is correct, the present results provide direct information concerning changes, that occur at the level of the single LGN unit, in response to binocular stimulus distortions stemming from chronic paralysis. However, even if two or more processes were operating, the present results identify properties of X- and Y-cells that are sufficiently flexible to contribute to the marked reduction in the X/Y ratio, characteristic of chronic paralysis. In either case, the fact that anesthesia-induced increases in the X/Y ratio are not seen in acute paralysis, nor in any other preparation, save that of chronic paralysis, suggests that at the very least, "priming" of LGN cells by a preparation such as chronic paralysis must occur before anesthesia-induced changes in the X/Y ratio can become manifest. The term "priming" refers to a tonic and systematic change in the sensitivity of X- and Y-cells to anesthesia. Since it is not possible to identify with certainty that exact nature of the processes which underlie this type of change, the concept of priming is useful as a means of referring to changes in the sensitivity of LGN units to anesthesia state induced by chronic paralysis without specifying the underlying process.

Given that chronic paralysis effects are mediated through mechanisms of binocular integration, any priming process, associated with monocular paralysis, would appear to stem from tonic activation of

one or more of these binocular mechanisms. However, on a conceptual level, one can see that binocular mechanisms such as those involved in stereoscopic depth perception and binocular fusion must operate phasically. One obvious reason for this is that binocular processes must occur in the context of continuous eye movements, resulting in rapid changes in the pattern of stimuli relating to binocular disparity and relative eye position.

In an attempt to characterize this priming process, the following questions will be addressed. First, how might such a phasic binocular mechanism operate upon LGN units in normal circumstances? Second, how would its impact be changed in acute paralysis (before priming), and in chronic paralysis (after priming)? Third, why should monocular paralysis prime the LGN for manifestation of anesthesia effects? Definitive answers to these questions, on the basis of the present results, are not possible. Therefore, a speculative approach to these questions will be adopted, using as an illustration a model developed by Singer (1977).

1) Phasic modulation in normal binocular fusion. An illustration of how a phasic binocular mechanism could operate in the LGN is provided by Singer (1977). In this model, corticothalamic projections control gating at the LGN level of signals from each eye, depending upon the degree of binocular disparity. The notion that signals are gated at the LGN in this fashion is based on the demonstration (Schmielau & Singer, 1974; 1977) that visual cortex facilitates (putatively through inhibition of intrinsic inhibitory interneurons) the transmission through the LGN of retinal signals from each eye, regarding a visual

target. However, this facilitation occurs only when the eyes are aligned so that the visual target falls upon exactly corresponding points on each retina. In these cases, when there is a minimum of binocular disparity, corticothalamic projections (which themselves receive binocular input) disable LGN intrinsic interneurons, which promote reciprocal inhibition between LGN cells receiving from the corresponding retinal points of each eye. This process leaves intact the reciprocal inhibition between signals from all other corresponding retinal loci, since binocular disparity in these cases, exceeds the cortical modulatory cells' disparity tolerances. Thus, retinal signals, concerning objects that fall in front of or behind the plane of fixation, remain fully subject to binocular inhibition at the LGN level, since these signals are too disparate to permit binocular fusion. According to Singer (1977), such a mechanism allows cortex to gate signal transmission through the LGN in a highly selective way, facilitating the transmission of information which produces a binocularly fused image, and allowing LGN intrinsic inhibition to cancel signals which would give rise to double images.

2) Manifestation of Anesthesia's Impact upon Binocular Processes, Before and After Priming. The relevance of Singer's (1977) model to the present discussion, lies in the fact that in a monocularly paralyzed animal, the requirements of a cortical "disparity analyzer" can be met in only a few of the many possible combinations of binocular alignment, since the position of one eye is fixed, and that of the other eye can vary freely. To the extent that moment-to-moment variation in the position of the mobile eye (with respect to the paralyzed eye) alters

the degree to which a mechanism such as that described by Singer (1977) impacts upon LGN cells receiving from homologous retinal points in each eye, variation in the excitability of these cells, related to suppression and facilitation of signal transmission, should occur. Since X-cells are more sensitive than Y-cells to binocular inhibitory processes (Suzuki & Takahashi, 1970; Fukada & Stone, 1976; Rodieck & Dreher, 1979), the phasic impact of this mechanism would be most readily observed as variation in the excitability of X-cells. However, in view of the reciprocal inhibitory interactions between X- and Y-cells (e.g., Singer & Bedworth, 1973), Y-facilitation, which compliments X-suppression (Experiment 3), could result from the fact that X-suppression removes a significant proportion of the inhibition that Y-cells typically receive from the X-system (Singer & Bedworth, 1973). Phasic activation of reciprocal X-suppression and Y-facilitation could therefore be observed as variation in the X/Y ratio, assuming that excitability changes underlie encounter rate changes, as suggested by the present results.

Anesthesia effects upon the acute X/Y ratio, as assessed by paired passes were highly variable, and in the aggregate, nonsignificant (Experiment 2). As stated earlier, this result could reflect the presence of residual tissue variance. However, the notion that prior to the chronic phase of paralysis, binocular mechanisms are phasic in character suggests an alternate interpretation of this variability. That is: 1) variation in the X/Y ratio is controlled by a mechanism similar to the one described by Singer (1977); 2) the activation/inactivation of this mechanism, on a moment-to-moment basis,

is itself controlled by the relative positions of the two eyes (or by the position of the mobile eye relative to that of the paralyzed eye in acute paralysis) and by the resulting pattern of binocular disparity; and 3) anesthesia disables the influence of this mechanism upon X- and Y-cells. Thus, in acute paralysis, when priming effects are absent or incomplete, phasic binocular mechanisms behave phasically. In this circumstance, manipulation of anesthesia state at a given point in time could produce changes in LGN unit excitability that depend less upon the type of cell than upon the degree to which a phasic binocular mechanism is concurrently engaged (as a consequence of momentary variations in the position of the mobile eye). This is similar to the way anesthesia manipulation would work in an animal with normal oculomotor function. When however, priming effects are complete, as is hypothesized to occur by the time that monocular paralysis becomes "chronic", the system then appears insensitive to momentary variations in relative eye position. In this circumstance, normally phasic mechanisms are engaged strongly, tonically, and unidirectionally (as a consequence of sufficient exposure to the distortions in binocular stimuli, that attend monocular paralysis). The differential influence of such binocular mechanisms upon X- and Y-cells then becomes evident, no longer obscured by the variability introduced by their phasic operation. Manipulation of anesthesia state could then produce excitability changes that are differential for X- and Y-cells such as those demonstrated in Experiment 3.

3) Monocular paralysis as a stilulus for the priming process? The description of Singer's model for normal binocular processes in the LGN,

in relation to possible alteration in its function in acute and chronic phases of monocular paralysis, is intended as an illustration of changes that could occur as a consequence of a priming process. It does not, however, provide insight into the manner in which chronic paralysis might initiate such a priming process, or what the process itself entails, although it appears that some aspect of a prolonged exposure to the distortions in retinal and nonretinal binocular stimuli that attend monocular paralysis must trigger the priming process. Since monocular paralysis effects are themselves considered as representative of adult neural plasticity (Brown & Salinger, 1975; Salinger et al., 1977a), these questions will be further considered in the context of adult neural plasticity.

The Present Results in Relation to the Concept of Neural Plasticity

As stated at the outset, neural plasticity refers to the brain's ability to alter an established pattern of responding, when cued by a significant change in the pattern of input. Formerly viewed as an exclusive characteristic of the developing organism (e.g. see Lynch et al., 1973; Steward et al., 1973; Lund, 1978; Greenough & Green, 1981), neural plasticity has been more recently observed to occur (albeit in a modified form) in the adult as well (Buchtel et al., 1975; Fiorentini & Maffei, 1974; Maffei and Fiorentini, 1976; Brown & Salinger, 1975; Hoffmann & Cynader, 1977; Salinger et al., 1977a; 1977b; Wilkerson et al., 1978; Kasamatsu, 1979; Kasamatsu et al. 1979; Salinger et al., 1980a; 1980b; Kasamatsu, Itakura & Johnsson, 1981; Garraghty et al., 1982; Kasamatsu, 1982; present results).

Structural and functional plasticity in the developing visual system is well documented (for reviews, see Rodieck, 1978; Stone et al., 1979; Lennie, 1980; Sherman & Spear, 1982). It is beyond the scope of the present discussion to describe in detail the wealth of information that has been uncovered concerning the physiological and anatomical sensitivities of the visual system during development. Rather, since the present results bear on the issue of adult neural plasticity, this discussion will center upon adult neural plasticity in binocular mechanisms (as revealed by monocular paralysis), and upon the sensitivity of these effects to manipulation of anesthesia state.

Are chronic paralysis effects evidence for adult, as distinct from infant, neural plasticity? Previous results argue that the answer to this question is "yes", since 1) the severe reduction in the X/Y ratio after chronic paralysis represents a substantial reorganization of typical LGN physiology (Salinger et al., 1977a; Garraghty et al., 1982); 2) neural plasticity associated with chronic paralysis occurs well into adulthood (Salinger et al., 1977a; Garraghty et al., 1982), and long after the close of any critical period thus far defined (e.g. see Sherman & Wilson, 1981); and 3) the adult LGN's response to monocular paralysis is different in character from neuroplastic changes in the immature LGN. That is, developmental plasticity is most evident in Y-cells (Hoffmann & Cynader, 1977; Hoffmann & Hollander, 1978; Kratz et al., 1978; Eyesel, Grusser & Hoffmann, 1979; Kratz, Sherman & Kalil, 1979; Sherman & Wilson, 1981; although see Mangel, Wilson & Sherman, 1983), whereas the effects of visual perturbation in the mature LGN are evident in X-cells (Brown & Salinger, 1975; Salinger et al.,

1977a, 1977b, 1978, Salinger, Garraghty, & Schwartz, 1980; Salinger, Garraghty, MacAvoy, & Hooker, 1980; Garraghty et al., 1982; present results) as well as Y-cells (Garraghty et al., 1982; present results). Further, monocular deprivation during the critical period reduces Y-cell encounter rates (e.g. see Sherman & Spear, 1982), while monocular paralysis, after the critical period increases Y-cell encounter rates (present results).

Is Adult Neural Plasticity Greater in X-cells than in Y-cells? Again, the answer to this question appears to be "yes", since the present results show that in addition to anesthesia's reciprocal influence upon the excitability of X- and Y-cells, X/Y differences are also evident both in terms of greater X-cell lability (i.e., more frequent anesthetic change, reversing or nonreversing, in either axon time or synapse time), and in the greater proportion of X-cells, relative to that of Y-cells, showing reversing changes in threshold (related to anesthesia manipulation). The fact that differences between X- and Y-cells in all three areas are far greater in chronic than in acute animals is consistent with the suggestion of Garraghty et al., (1982) that a chronic duration of monocular paralysis alters the degree to which X- and Y-cells are affected by binocular inhibition.

The observation that X-cells may be more labile than Y-cells in their responses to both monocular paralysis and anesthesia manipulations may have implications for theories concerning the functional significance of X/Y differences (e.g., see Lennie, 1980). Greater lability of X- relative to Y-cells may be attributable to particular subpopulations of X-cells such as the one tentatively identified here

(see results), although a definite conclusion of this sort would be premature at this time. At the least, however, these results clearly call for a more quantitative assessment of the anesthetic sensitivities of X- and Y-cells. This is true for all measures of the kind used in this study, but particularly for those that relate to excitability. For example one measure not taken from units in the present study was unit baseline firing rate. Although baseline firing rate of an LGN unit, unlike its transfer ratio, may not be positively correlated with level of excitability, its inclusion with a battery of other excitability measures might prove informative.

Neural plasticity in mechanisms underlying binocular integration. The active, reversible nature of the LGN's response to chronic monocular paralysis (Schroeder & Salinger, 1978; Salinger, Garraghty, & Schwartz, 1980; Garraghty et al., 1982; present results) suggests that the changes in LGN unit properties may be a functional response to alteration of input, rather than a degenerative or atrophic response to injury. It may be that the brain's response to the retinal and nonretinal binocular distortions associated with monocular paralysis effectively maximizes its remaining binocular visual capacity by suppressing signal processing in the X-system and enhancing signal processing in the Y-system. The X-system has higher spatial frequency sensitivity than the Y-system (Wilson et al., 1976; Kratz et al., 1978; Bullier & Norton, 1979), and summates photic stimulation in a more linear fashion (Hochstein & Shapley, 1976). Binocular integration of X-mediated, relative to Y-mediated information, would therefore be more severely affected by monocular defocussing and misalignment of the

visual axes after monocular paralysis. Selective suppression of the X-system could substantially reduce confusion stemming from a high degree of abnormal binocular disparity. The Y-system has lower spatial frequency requirements (Lennie, 1980), depends less upon linear summation of photic stimulation (Hochstein & Shapley, 1975, 1976), and has a greater representation of peripheral visual space (Hoffmann et al., 1972; Garraghty et al., 1982). Facilitation of the Y-system after chronic monocular paralysis would simply provide the geniculostriate pathway with as much visual information as posssible from the system that is least disrupted by the stimulus distortions associated with monocular paralysis. In any case, since X-cells do not project into the tectopulvinar system, but Y-cells do (Lennie, 1980), X-suppression and Y-facilitation would leave intact (and might even enhance) the gross pattern analysis and visual orienting capacities that rely upon this system (Goldberg & Robinson, 1978).

The notion that the changes in the LGN after monocular paralysis may be a functional response to distortion of visual input suggests that adult plasticity may prolong or perhaps re-introduce the flexibility of the immature system (albeit in a modified fashion). Such flexibility would enable the binocular processes of the visual system to accommodate to the sometimes radical input changes that accompany injury and aging, and to maintain some capacity for binocular fusion throughout. This possibility is consistent with the observation that monocular enucleation in adult cats reinstates the capacity to recover from the effects of early (within the critical period) monocular deprivation (Hoffmann & Cynader, 1977).

Although neural plasticity is generally considered to be a result of major structural/functional reorganization of neural circuits, it is also possible, however, that the changes in the LGN X/Y ratio after chronic paralysis are actually not reflective of such an organizational change. In this view, the changes after chronic paralysis would reflect the activity of normal binocular mechanisms, whose inherent flexibility permits them to be engaged by monocular paralysis in a fashion that promotes tonic suppression of X-cells and facilitation of Y-cells. Whether or not the response of the mature LGN to chronic paralysis is considered plastic in the sense of change in organization, as opposed to change in output, the degree of plasticity exhibited by binocular mechanisms, here and in earlier studies, suggests that such mechanisms may provide an ideal system for analysis of adult neural plasticity.

Methodological implications of anesthesia effects. In adult cats, neuroplastic responding after monocular paralysis, is found in LGN (Brown & Salinger, 1975; Salinger et al., 1977a; Garraghty et al., 1982; present results), and in cortex (Fiorentini & Maffei, 1974, Buchtel et al., 1975; Maffei & Fiorentini, 1976). Anesthesia reverses monocular paralysis effects, both in LGN (Garraghty et al., 1982; present results), and perhaps in cortex (see Garraghty et al., 1982). The fact that anesthesia effects upon the X/Y ratio have not been observed in any context, save that of monocular paralysis, can be explained in two ways. First, it may be that the possibility of such effects has not been properly examined. This could imply that the failure to observe monocular deprivation effects in the adult LGN (e.g., see Hubel & Wiesel, 1970; Sherman & Wilson, 1981) may result from the

fact that these investigators recorded data from deeply anesthetized subjects. Further and most importantly, the state of the immature visual system after monocular and binocular deprivation (see review by Sherman & Spear, 1982), might be radically different if subjects had been recorded unanesthetized.

A second possible explanation is that as an adult research preparation, monocular paralysis is unique, and that anesthesia state simply has no impact in adult preparations which do not involve monocular paralysis, or an equivalent manipulation. This would suggest that it is the brain's response to monocular paralysis which permits manifestation of anesthesia effects upon the X/Y ratio. The following section will treat this possibility.

How does monocular paralysis promote neuroplastic responding? This question is equivalent to one raised earlier, but deferred until now. That is, "How does monocular paralysis stimulate a priming process?" In a one-process view (i.e., anesthesia reverses the process initiated by monocular paralysis - see above), the priming process would be a systematic suppression of X-cell excitability and an enhancement of Y-cell excitability. The way that monocular paralysis could stimulate such a process has not yet been fully explored; however, it is possible to speculate on this matter.

One possibility is raised by the observation that pretreatment with the neurotoxin 6-hydroxydopamine (6OHDA) prevents the reduction in the X/Y ratio characteristic of chronic monocular paralysis (Guido et al., 1982). The fact that 6OHDA appears relatively selective to noradrenergic neurons (Kasamatsu & Pettigrew, 1976; Kasamatsu,

Pettigrew & Ary, 1979), suggests that chronic paralysis effects may depend upon activation of noradrenergic systems. Thus, anesthesia effects, which are observed only after chronic paralysis (Garraghty et al., 1982; present results), may also depend upon activation of noradrenergic systems. At the present time, there is no evidence that either pentobarbital or nitrous oxide impacts directly upon noradrenergic neurons. Such a direct interaction, however, is not required, since there are a variety of loci at which these anesthetics could indirectly disable the impact of noradrenergic activity.

If noradrenergic activation is critical to chronic paralysis and to anesthesia effects, the fact that neither type of effect is evident until two weeks after the onset of paralysis suggests that the noradrenergic response to monocular paralysis is sluggish. This suggestion is consistent with the notion that processes of change which rely upon noradrenergic systems may be characteristically sluggish. The "sluggish" or "delayed" character of noradrenergic responses is suggested by the common observation that the psychotherapeutic effects of drugs which target catecholamine (including noradrenergic) systems generally require two or more weeks of continued administration to become manifest (Cooper et al., 1978).

It is not clear which stimulus feature(s) of monocular paralysis would be critical for noradrenergic activation. However, distortion in the binocular pattern of proprioception is a likely candidate for several reasons. First, the initial central target of ocular proprioceptive stimuli is the mesencephalic nucleus of Cranial Nerve V, a structure intrinsic to the reticular formation (Fillenz, 1955; Batini

et al., 1975; Alvarado-Mallart et al., 1975; Abrams & Anastee, 1977). Second, as discussed previously, the reticular formation appears critical in the mediation of both monocular paralysis and anesthesia effects upon the LGN. Third, noradrenergic systems, which have been implicated in the manifestation of adult neural plasticity in the LGN (Guido et al., 1982), and in visual cortex (Pettigrew & Kasamatsu, 1978; Kasamatsu & Pettigrew, 1979; Kasamatsu, 1979; Kasamatsu et al., 1981; Johnsson & Kasamatsu, 1983; Shirokawa & Kasamatsu, 1984), originate in the locus coeruleus and pontine tegmentum (Moore & Bloom, 1979), structures lying in the pontine division of the reticular formation. Thus, it may be that disruption of binocular proprioceptive stimuli, because of some preferential access to the reticular formation and to its noradrenergic ramifications, is sufficient to promote a manifestation of neural plasticity, and in turn, of anesthesia effects.

The apparent dependence of neuroplastic responding and of anesthesia effects in adults, upon prior noradrenergic activation, may have a parallel in developmental plasticity. Sustained noradrenergic activation does appear critical in developmental plasticity, since 1) cortical microperfusion with norepinephrine restores cortical plasticity in kittens formerly treated with 6OHDA (Pettigrew & Kasamatsu, 1978; Kasamatsu et al., 1979), and 2) a tight, quantitative relationship has been observed between the density of beta adrenergic receptors in cortex and the degree of plasticity in response to monocular lid suture during the critical period (Johnsson & Kasamatsu, 1983; Shirokawa & Kasamatsu, 1984). The possible dependence of systematic anesthesia effects upon the level of activity in noradrenergic systems (see above) further

supports the suspicion that the consequences of developmental manipulations in the visual system may be radically altered, if data are recorded from unanesthetized subjects.

This account is admittedly speculative. However, several of its implications concerning the impact of anesthesia in common vision research paradigms merit repetition and emphasis. First, in the presence of any experimental manipulation sufficient to induce adult neuroplastic response (e.g. monocular paralysis, monocular enucleation, noradrenergic microperfusion), level of anesthesia should be systematically controlled, since it can significantly influence the pattern of results (Garraghty et al., 1982; present results). Secondly, any manipulation that disables (or counteracts) the action of the reticular-adrenergic system (e.g., anesthesia induction or application of 6OHDA) should produce a blockade of adult plasticity. Finally, in developmental paradigms, the impact of any stimulus modification is potentially affected by the level of anesthesia during data recording.

Ophthalmological Implications of the Present Results

Monocular paralysis can be viewed as an animal model for a human visual impairment known as strabismic amblyopia. In strabismic amblyopia, one eye is misaligned relative to the other. With prolonged exposure to misalignment of the visual axes, the brain suppresses the input from the deviated eye, resulting in moderate to severe loss of vision, and/or severe reduction in binocular function and stereopsis (Duke-Elder, 1973; see Jampolsky, 1980; Von Norden, 1980 for recent in-depth reviews). Previous research has demonstrated a strong parallel

between monocular paralysis in cats, and strabismic amblyopia in humans.

First, in both strabismic amblyopia and monocular paralysis, there is a unilateral oculomotor deficit, with one eye affected and the other normal. The visual axis in the affected eye is deviated with respect to that of the other, which greatly reduces or even abolishes the ability to align both eyes upon a single target.

Second, in strabismic amblyopia, ocular misalignment produces an active process of visual suppression (Von Norden, 1980; Sireteneau & Fronius, 1981), which is binocular in nature (Sireteneau & Fronius, 1981). Even after prolonged ocular misalignment, this process is at least partially reversible, with additional input alteration provided by orthoptic devices such as eye patches or prism goggles (Von Norden, 1980). Likewise in monocular paralysis, ocular misalignment triggers an active process, believed to be one of binocularly mediated suppression (see Garraghty et al., 1982), which is partially reversible, with additional input alteration (Schroeder & Salinger, 1978).

Third, strabismic amblyopia involves both a loss of acuity, confined to central visual space (Hess, Campbell & Zimmern, 1980; Sireteneau & Fronius, 1981), and a perimetric deficit, which affects both peripheral visual fields (Sireteneau & Singer, 1984). One corresponding "deficit" in monocular paralysis is neurophysiological, a reduction in the X/Y ratio, which is not necessarily equivalent to an acuity loss, but which is confined to central visual space (Garraghty et al., 1982). Another is behavioral, a bilateral perimetric deficit (Garraghty, Salinger & MacAvoy, 1978).

Results obtained with the monocular paralysis preparation appear to have implications for amblyopia in a number of areas: 1) information on the stimulus features of oculomotor asymmetry, which may be critical to the initiation and maintenance of visual deficits; 2) elucidation of the nature of changes in the geniculostriate pathway that could underlie amblyopic deficits; and 3) indirect support for the notion that amblyopic deficits may be amenable to pharmacologic intervention.

Critical stimulus features in amblyopia. Research with monocular paralysis has shown that the reduction in the X/Y ratio after chronic paralysis is a result of both retinally and nonretinally mediated cues (Salinger et al., 1977b; 1980a). Retinally mediated stimuli have been shown to be important in strabismic amblyopia (Duke-Elder, 1973; Von Norden, 1980; Sireteneau & Fronius, 1981), but the nonretinal (proprioceptive) consequences of ocular misalignment have received little attention. Extraocular proprioception has been shown to be involved in the spatial localization of visual targets (Steinbach & Smith, 1981), but its contribution to amblyopic deficits in strabismus is presently unclear. In view of the parallel between the effects of strabismus and those of monocular paralysis, the possible involvement of nonretinal binocular distortions in strabismic amblyopia merits further attention.

Neural changes underlying amblyopia. Amblyopic deficits associated with strabismus are believed to result from some form of centrally mediated suppression (e.g. see Von Norden, 1980; Sireteneau & Fronius, 1981). Research with monocular paralysis has revealed that paralysis-induced changes occur in the LGN--reduction in the X/Y ratio

(Brown & Salinger, 1975; Salinger et al., 1977a; Garraghty et al., 1982), and in visual cortex--reduction in the number of binocular units (Fiorentini & Maffei, 1974; Maffei & Fiorentini, 1976). Although the relationship between changes in LGN and in cortex after monocular paralysis is presently unclear, these findings do suggest loci at which processes which lead to visual suppression in amblyopia could occur. Moreover, the present results suggest that in the LGN, suppression of X-cell activity and facilitation of Y-cell activity may underlie the X/Y ratio reduction after chronic paralysis. This interpretation, although constrained by any deficiency in the model used here (see above), is of particular interest in view of the strong parallel between the chronic paralysis preparation and strabismic amblyopia, outlined above.

One deficit noted in strabismic amblyopia is a loss of acuity (Hess et al., 1980; Sireteneau & Fronius, 1981). In this regard, suppression of X-cells (after chronic paralysis - present results) may be a significant factor, since X-cells appear to subserve high frequency acuity (e.g., see Lennie, 1980), and since some reports suggest a relationship between X-cell dysfunction and acuity loss (Ikeda & Wright, 1976; Ikeda & Tremain, 1979). Unfortunately, however, a loss of acuity in association with X-cell suppression after chronic paralysis has not yet been explored.

It is not clear how facilitation of Y-cell activity, which the present results suggest may also be a consequence of chronic paralysis (present results), would contribute to a loss of high spatial frequency sensitivity, since Y-cells are sensitive to lower spatial frequencies (e.g., see Lennie, 1980). However, the fact that the physiology of <u>both</u>

X- and Y-cells appears altered after monocular paralysis (present results) suggests that in addition to abnormal binocular interactions in amblyopia (Hess et al., 1980; Sireteneau & Fronius, 1981), there may also be abnormal interaction between X- and Y-systems. Along these lines, Hess (1982) has recently advanced another hypothesis concerning the nature of visual deficits in amblyopia. Hess (1982) reported a deficit in amblyopes which he refers to as "Jumbled Vision", or the inability to analyze the phase relationships between stimuli of differing spatial frequencies (e.g., a given fundamental and its third harmonic) in a complex visual display. In fact, Hess (1982) suggested that since for strabismics under normal viewing conditions, this deficit may be far more powerful than acuity loss, the term "Tarachopia" (jumbled or confused vision) should be substituted for "Amblyopia" (blunt vision). This conceptualization of amblyopic deficits notes that 1) in normal subjects, stimuli of markedly different spatial frequencies (such as a given fundamental and its third harmonic) are processed through completely independent spatial frequency channels (Graham & Nachmias, 1971; Lawden, 1982); and 2) in amblyopes, inability to resolve phase relationships between a fundamental and its third harmonic may result from abnormal interactions between the spatial frequency channels which process these stimuli (Lawden, 1982). This possibility is particularly interesting in light of the present results, since 1) X- and Y-cells are sensitive to stimuli of quite different spatial frequencies (e.g. see Lennie, 1980); and 2) given that the one-process interpretation of these results is correct, tonic reciprocal changes in the excitability of <u>both</u> X- and Y-cells are induced by chronic

paralysis. These excitability changes would necessarily distort the nature of typical interactions between X- and Y-systems (e.g., reciprocal X/Y inhibition, Singer & Bedworth, 1973).

Pharmacological sensitivity of mechanisms underlying amblyopia. A final aspect of results obtained with monocular paralysis is the pharmacological sensitivity of monocular paraysis effects. Prior treatment with a neurotoxin which targets the brain's catecholamine systems, 6OHDA, prevents the reduction in the LGN X/Y ratio which typically follows chronic paralysis (Guido et al., 1982). Further, anesthesia, induced with either pentobarbital (Garraghty et al., 1982) or nitrous oxide (present results) immediately reverses the impact of chronic paralysis upon the LGN. Finally, the fact that the one experiment which failed to observe the cortical impact of monocular paralysis (Berman, Murphy & Salinger, 1979), was one in which data were recorded from deeply anesthetized animals, suggests that monocular paralysis effects in cortex, like those in the LGN, are pharmacologically reversable. In view of the parallel between the monocular paralysis preparation and strabismic amblyopia, these considerations support the idea that amblyopic deficits may also respond to pharmacological intervention. This possibility is consistent with clinical observations concerning the pharmacological sensitivity of 1) ocular alignment mechanisms and 2) binocular information processing mechanisms.

First, in regard to ocular alignment mechanisms, characteristically different patterns of oculomotor activity (Cohen, 1975), and eventual relaxation of oculomotor alignment mechanisms (Jampolsky, 1980) attend

various planes of surgical anesthesia. Second and more importantly, improvements in impaired ocular convergence are produced by both ethanol (Cohen and Alpern, 1969) and barbiturates (Westheimer, 1963) at dose levels far below those required for anesthesia induction. While the pharmacological basis of these effects was not known during the course of these early experiments, it did appear that binocular mechanisms underlying conjugate eye movements exhibit exquisite dose-response sensitivity. More recent reports suggest that barbiturates (and perhaps other CNS depressants also) impact at the cellular level by potentiating or mimicking the effects of gamma aminobutyric acid (GABA), which is widely used as a neurotransmitter, in inhibitory synapses throughout the CNS (Krnjevic et al., 1966; Barker & Mathers, 1981; Hendrickson, 1984). This new information raises the hope that other, more specific drugs which also target GABA-ergic mechanisms, may be used to offset maladaptive ocular alignment in strabismus, at lower dosages than those used previously, and with fewer side effects than barbiturates or alcohol. One such agent is chlordiazepoxide (librium). It has been proposed by Nicoll & Wojtowicz (1980) that compounds of this class (benzodiazepines) may facilitate the action of GABA by simultaneous stimulation of "endogenous benzodiazepine" receptors, present in some GABA-ergic synapses. Before these pharmacological properties were suspected, chlordiazepoxide was used by Fletcher (1961), who reported significant improvement of impaired ocular alignment in strabismic amblyopes. Unfortunately, this intriguing result was not pursued further. However, chlordiazepoxide and related compounds, are considered more specific (chemically) than barbiturates, and carry less

risk of tolerance/dependence (Goth, 1981). Thus, they provide a potentially useful avenue for treatment of ocular misalignment in strabismus.

Another potential for pharmacological intervention concerns the deficits in binocular information processing, which stem from long term ocular misalignment in strabismus (Sireteneau & Fronius, 1981). Processing of binocular stimuli relies upon GABA-ergic mechanisms at many levels in the visual system (topic reviewed by Hendrickson, 1984). Thus, drugs which target GABA-ergic synapses such as barbiturates and the more specific benzodiazepines (see above) may help to offset the deficits in binocular processing which result from ocular misalignment. In fact, Fletcher (1961) reported an improvement in the capacity for binocular fusion in strabismics treated with chlordiazepoxide. At the time, this effect could have been interpreted as due to improvement in ocular misalignment. More recent evidence, however, suggests that chlordiazepoxide disabled, partially or completely, the mechanism promoting fusional impairment in amblyopia, since after prolonged strabismus, capacity for binocular fusion does not improve simply as a consequence of correcting ocular misalignment (Von Norden, 1980).

The fact that amblyopic defects in the central visual pathways appeared to be reduced by chlordiazepoxide is in parallel to the observations that amblyopia-like effects in the LGN are reversed by anesthetics (Garraghty et al., 1982; present results). Further, chlordiazepoxide, or other benzodiazepines, may also reduce the influence of noradrenergic activity (Cooper et al., 1978), which, as discussed above, may be critical to the production of chronic paralysis

effects. These propositions could be directly tested by administration of benzodiazepines to chronic monocularly paralyzed animals, with the prediction being that such agents would abolish the reduction in the X/Y ratio (stemming from chronic paralysis), or at least decrease its severity. To the extent that the parallel between chlordiazepoxide effects in amblyopia and anesthesia effects in monocular paralysis is more than coincidental, these considerations suggest an additional avenue for pharmacological analysis and treatment of amblyopia--manipulation of noradrenergic mechanisms. Thus, given that the processes underlying amblyopic deficits are at all similar to those underlying monocular paralysis effects in LGN and in cortex, amblyopia, like monocular paralysis effects, may reverse with the appropriate chemical agents. In view of the plethora of increasingly specific pharmacological agents currently under development, such a hope does not seem unrealistic.

BIBLIOGRAPHY

Abrams, V.C., & Anastee, G. (1977). Units in the superior colliculus and underlying tegmental structures responding to passive eye movement. Journal of physiology (London), 272, 91-92.

Alvarado-Mallart, Batini, C., Buisseret-Delmas, K., & Corvisier, J. (1975). Trigeminal representation of the masticatory and extraocular proprioceptors as revealed by horseradish peroxidase retrograde transport. Experimental Brain Research, 23, 167-179.

Anderson, J. & Essick, P. (1984). Convergence of visual and proprioceptive information in posterior parietal cortex. Paper presented at the Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, Florida.

Barker, J., & Mathers, D. (1981, January). GABA receptors and the depressant action of pentobarbital. Trends in Neuroscience, pp. 10-13.

Batini, C., Buisseret, P., & Buisseret-Delmas, C. (1975). Trigeminal pathway of the extrinsic eye muscle afferents in cat. Brain Research, 83, 74-78.

Berman, N., Murphy, H., & Salinger, W. (1979). Monocular paralysis in the adult cat does not change cortical ocular dominance. Brain Research, 164, 290-293.

Bishop, P.O. Burke, W., & Davis, R. (1962). The identification of single units in central visual pathways. Journal of Physiology, 162, 409-431.

Bishop, P.O., Clare, M., & Landau, W. (1969). Further analysis of fiber groups in the optic tract. Experimental Neurology, 24, 386-399.

Bowsher, D. (1970). Reticular projections to the lateral geniculate in cat. Brain Research, 23, 247-249.

Bowsher, D. (1975). Diencephalic projections from the midbrain reticular formation. Brain Research, 95, 211-220.

Brown, D.L., & Salinger, W.L. (1975). Loss of X-cells in the lateral geniculate nucleus with monocular paralysis: Neural plasticity in the adult cat. Science, 189, 1011-1012.

Buchtel, H.A., Berlucchi, G., & Mascetti, G.G. (1975). Behavioral and electrophysiological analysis of strabismus in cats. INSERM, 43, 27-44.

Buisseret, P., & Maffei, L. (1977). Extraocular proprioceptive projections to visual cortex. Experimental Brain Research, 28, 421-425.

Bullier, J., & Henry, G.H. (1979). Neural path taken by afferent streams in striate cortex of the cat. Journal of Neurophysiology, 42, 1264-1270.

Bullier, J., & Norton, T.T. (1979). X and Y relay cells in cat lateral geniculate nucleus: Quantitative analysis of receptive-field properties and classification. Journal of Neurophysiology, 42, 244-273.

Burke, W. & Cole, A. (1978). Extraretinal influences on the lateral geniculate nucleus. Review of Physiology, Biochemistry and Pharmacology, 80, 105-166.

Chalupa, L., Macadar, A., & Lindsley, D.B. (1975). Response plasticity of lateral geniculate neurons during and after pairing of auditory and visual stimuli. Science, 190, 290-292.

Cleland, B., & Dubin, M. (1977). Organisation of visual inpute to interneurons of the lateral geniculate nucleus of the cat. Experimental Brain Research, Supplement 1, 493-496.

Cleland, B., Dubin, M., & Levick, W. (1971). Sustained and transient neurons in the cat's retina and lateral geniculate nucleus. Journal of Physiology (London), 306-310.

Cleland, B.G., Levick, W.R., Morstyn, R., & Wagner, H.G. (1976). Lateral geniculate relay of slowly conducting retinal afferents to cat visual cortex. Journal of Physiology, 255, 299-320.

Cohen, P.J. (1975). Signs and stages of anesthesia. In L. Goodman and A. Gilman (Eds.) The pharmacological basis of therapeutics. (pp. 60-65). New York: Macmillan.

Cohen, M., & Alpern, M. (1969). Vergence and acommodation. VI. The influence of ethanol on the AC/A ratio. Archives of Ophthalmology, 81, 518.

Cohen, B., & Feldman, M. (1968). Relationship of elcetrical activity in the pontine reticular formation and lateral geniculate body to rapid eye movements. Journal of Neurophysiology, 31, 806-817.

Cohen, B., Feldman, M., & Diamond, S. (1969). Effects of eye movements, brainstem stimulation and alertness on transmission through the lateral geniculate body of the monkey. Journal of Neurophysiology, 32, 583-594.

Cooper, J., Bloom, F., & Roth, R. (1978). The Biochemical Basis of Neuropharmacology. New York: Oxford University Press.

Daniel, W.W. (1978). Applied Nonparametric Statistics, Boston: Houghton Mifflin.

Darbinjar, T.M., Golovchinsky, V.B., & Plehotkina, S.I. (1971). Effects of anesthetics on reticular and cerebral activity. Anesthesiology, 34, 219.

Donaldson, I. (1979, July). Response in cat suprasylvian cortex (Clare-Bishop Area), to stretch of the extra ocular muscles. Proceedings of the Physiological Society, 589-602.

Donaldson, I., & Dixon, M. (1980). Excitation of units in LGN and contiguous nuclei of the cat by stretch of extrinsic ocular muscles. Experimental Brain Research, 38, 245-255.

Dubin, M. & Cleland, B. (1977). The organization of visual inputs to interneurons of the lateral geniculate nucleus of the cat. Journal of Neurophysiology, 40, 410-427.

Duke-Elder, S. (1973). System of ophthalmology. Ocular motility and strabismus, St. Louis: Mosby.

Eisman, J., Hansen, S., & Burke, W. (1967). Synaptic responsiveness in the lateral geniculate nucleus of the alert cat. Vision Research, 7, 385-399.

Eysel, U.Th., Grusser, O.-J., and Hoffmann, K.-P. (1979). Monocular deprivation and the signal transmission by X- and Y-neurons in the lateral geniculate nucleus. Experimental Brain Research, 34, 521-539.

Fernald, R., & Chase, R. (1971). An improved method for plotting retinal landmarks and focussing the eyes. Vision Research, 11, 95-96.

Fillenz, M. (1955). Responses in the brainstem of the cat to stretch of extrinsic ocular muscles. Journal of Physiology (London), 128, 182-199.

Fiorentini, A. & Maffei, L. (1974). Change in the binocular properties of the simple cells of the cortex in adult cats following immobilization of one eye. Vision Research, 14, 217-218.

Fiorentini, A., Maffei, L., & Bisti, S. (1979). Change in the binocular properties of cortical cells in the cental and paracentral visual field projections of monocularly paralyzed cats. Brain Research, 127, 153-158.

Fletcher, M. (1961). Chlordiazepoxide (Librium) in the treatment of strabismus. A preliminary report. Journal of the American Medical Womens' Association, 16, 37.

Foote, W., Maciewicz, R., Mordes, J. (1974). Effect of midbrain raphe and lateral mesencephalic stimulation on spontaneous and evoked activity in the lateral geniculate of the cat. Experimental Brain Research, 19, 124-130.

Foote, W., Mordes, J., Colby, C., & Harrison, T. (1977). Differential effect of midbrain stimulation on X-sustained and Y-transient neurons in the lateral geniculate nucleus of the cat. Brain Research, 127, 153-158.

Friedlander, M., Lin, R., Stanford, D., & Sherman, M. (1981). Morphology of functionally identified neurons in lateral geniculate nucleus of the cat. Journal of Neurophysiology, 46, 80-129.

French, J.D., Verzeano, M., & Magoun, H.W. (1953). A neural basis of the anesthetic state. Archives of Neurology and Psychiatry, 69, 519.

Fukada, Y. (1976). Receptive field organization of cat optic nerve fibers with special reference to conduction velocity. Vision Research, 209-226.

Fukada, Y., & Stone, J. (1976). Evidence of differential inhibitory influences on X- and Y-type relay cells in the cat's lateral geniculate nucleus. Brain Research, 113, 188-196.

Garraghty, P., Salinger, W., & MacAvoy, M. (1978). Perimetric deficits associated with chronic monocular paralysis. Paper presented at Society for Neurosciences, 8th annual meeting, St. Louis, November.

Garraghty, P.E., Salinger, W.L., MacAvoy, M.G., Schroeder, C.E., & Guido, W.G. (1982). The shift in X/Y ratio after chronic monocular paralysis: A binocularly mediated, barbiturate-sensitive effect in the adult lateral geniculate nucleus. Experimental Brain Research, 47, 301-308.

Gilbert, C., & Kelly, J. (1975). The projections of cells in different layers of the cat's visual cortex. Journal of Comparative Neurology, 175, 81-105.

Goldberg, M., & Robinson, D.L. (1978). Visual system: Superior colliculus. In R.B. Masterson (Ed.), Handbook of behavioral neurobiology. (pp. 119-164). New York: Plenum.

Goodman, S., & Mann, P. (1967). Reticular and thalamic multiple unit activity during wakefulness, sleep and anesthesia. Experimental Neurology, 19, 11-24.

Goth, A. (1981). Medical Pharmacology: Principles and Concepts. St Louis: Mosby.

Graham, N., & Nachmias, J. (1971). Detection of grating patterns containing two spatial frequencies: A comparison of single channel and multichannel modes. Vision Research, 11, 251-259.

Greenough, W., & Green, E. (1981). Experience and the changing brain. In J. March & S. Kiesler (Eds.), Aging: Biology and behavior. (pp.159-200). New York: Academic Press.

Guido, W.B., Salinger, W.L., & Schroeder, C.E. (1982). Pharmacological blockade of the effects of chronic monocular paralysis. Paper presented at the Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, Florida.

Guillery, R.W. (1967). Patterns of fiber degeneration in the dorsal lateral geniculate nucleus following lesions in visual cortex. Journal of Comparative Neurology, 130, 197-222.

Hendrikson, A. (1984). Localization of neurotransmitters in visual cortex. Investigative Ophthalmology and Visual Science, 25 no.3 (suppl), 165.

Hess, R. (1982). Developmental sensory impairment: Amblyopia or Tarachopia. Human Neurobiology, 1, 17-30.

Hess, R., Campbell, F., & Zimmern, R. (1980). Differences in the neural basis for human amblyopia: the effect of mean luminance. Vision Research, 20, 295-305.

Hillyard, S.A., & Picton, T.W. (1979). Conscious perception and cerebral event related potentials. In J.E. Desmedt (Ed.) Progress in Clinical Neurophysiology: Vol. 6. Cognitive components in cerebral event related potentials and selective attention. (pp. 1-52). Karger: Basel.

Hochstein, S., & Shapley, R.M. (1976). Quantitative analysis of retinal ganglion cell classifications. Journal of Physiology (London), 262, 237-264.

Hoffmann, K.-P., & Cynader, M. (1977). Functional aspects of plasticity in the visual system after early monocular deprivation. Philosophical Transactions of the Royal Society of London (Biology), 278, 411-424.

Hoffmann, K.-P., & Hollander, H. (1978). Physiological and morphological changes in cells of the lateral geniculate nucleus in monocularly deprived and reverse sutured cats. Journal of Comparative Neurology, 177, 145-158.

Hoffmann, K.-P., Stone, J., & Sherman, S.M. (1972). Relay of receptive field properties in dorsal lateral geniculate nucleus of the cat. Journal of Neurophysiology, 35, 518-531.

Hollander, H. (1970). The projection from the visual cortex to the lateral geniculate body (LGB). An experimental study with silver impregnation methods in the cat. Experimental Brain Research, 10, 219-235.

Hollander, H. (1972). Projection of the visual cortex to the lateral geniculate nucleus in the cat. In T. Frigyesi, E. Rinvik, & M.D Yahr (Eds.) Corticothalamic projections and sensorimotor activities, (pp. 475-484). New York: Raven.

Hollander, H., & Martenez-Millan, L. (1975). Autoradiographic evidence for a topographically organized projection from striate cortex to the lateral geniculate nucleus in the rhesus monkey. Brain Research, 100, 407-411.

Hollander, H., & Vanegas, H. (1977). The projection from the lateral geniculate nucleus onto the visual cortex in the cat: A quantitative study with horseradish peroxidase. Journal of Comparative Neurology, 173, 519-536.

Ikeda, H., & Wright, K. (1976). Properites of LGN cells in kittens reared with convergent squint: a neurophysiological demonstration of amblyopia. Experimental Brain Research, 25, 63-77.

Ikeda, H., & Tremain, K. (1979). Amblyopia occurs in retinal ganglion cells in cats reared with convergent squint without alternating fixation. Experimental Brain Research, 35, 559-582.

Jampolsky, A. (1978). Unequal inputs and strabismus management: A comparison of human and animal strabismus. In Symposium on strabismus: Transactions of the New Orleans Academy of Ophthalmology, (pp. 148-212). St. Luis: Mosby.

Johnsson, G., & Kasamatsu, T. (1983). Maturation of monoamine neurotransmitter receptors in the cat. Experimental Brain Research, 50, 449-458.

Jones, E. (1975). Some aspects of the organization of the thalamic reticular complex. Journal of Comparative Neurology, 162, 285-308.

Kasamatsu, T. (1979). Involvement of the Beta adrenergic receptor in cortical plasticity. Investigative Ophthalmology and Visual Science (Supplement 1), 18, 135.

Kasamatsu, T. (1982). Neuronal plasticity maintained by the central norepinephrine system in the cat visual cortex. In A. Epstein and J. Sprague (Eds.) Progress in Psychobiology and Physiological Psychology (Vol. 10), New York: Acedemic Press.

Kasamatsu, T., & Pettigrew, J. (1976). Depletion of brain catecholamines: Failure of ocular dominance shift after monocular occlusion in kittens. Science, 194, 206-209.

Kasamatsu, T., Pettigrew, J.D., & Ary, M. (1979). Restoration of visual cortical plasticity by local microperfusion with norepinephrine. Journal of Comparative Neurology, 185, 163-182.

Kasamatsu, T., Itakura, T., & Johnsson, G. (1981). Intracortical spread of exogenous catecholamines: Effective concentration for modifying cortical plasticity. Journal of Pharmacology and Experimental Therapeutics, 217, 841-850.

Kawamura, S., Sprague, J.M., & Nimi, K. (1974). Cortical projections from the cortices of the thalamus, pretectum and superior colliculus in the cat. Journal of Comparative Neurology, 158, 339-362.

Kratz, K.E., Webb, S.V., & Sherman, S.M. (1978). Electrophysiological classification of X- and Y-cells in the cat's lateral geniculate nucleus. Vision Research, 18, 489-492.

Krnjevic, K., Randic, M., & Straughn, D.W. (1966). Pharmacology of cortical inhibition. Journal of Physiology, 184, 78-105.

Lamarre, Y., Filion, M., & Cordeau, J. (1971). Neuronal discharges in the ventrolateral nucleus of the thalamus during sleep and wakefulness in the cat: I. Spontaneous activity. Experimental Brain Research, 12, 480-496.

Laurent, J.-P., & Guerrero, F.A. (1975). Reversible suppression of ponto-geniculo-occipital waves by localized cooling during paradoxical sleep in cats. Experimental Neurology, 49, 356-369.

Lawden, M. (1982). Analysis of spatial phase in amblyopia. Human Neurobiology, 1, 74-86.

Leger, L., Sakai, K., Salvert, T., Touret, M., & Jouvet, M. (1975). Delineation of dorsal lateral geniculate afferents from the cat brainstem as visualized by the horseradish peroxidase technique. Brain Research, 93, 490-496.

Lennie, P. (1980). Parallel visual pathways. Vision Research, 20, 561-594.

Lindstrom, S. (1982). Synaptic organization of inhibitory pathways to principal cells in the lateral geniculate nucleus of the cat. Brain Research, 284, 447-453.

Lund, R. (1978). Development and plasticity of the brain: An introduction, New York: Oxford Univ. Press.

Lynch, G., Stanfield, B., & Cotman, C. (1973). Developmental differences in post-lesion axonal growth in the hippocampus. Brain Research, 59, 155-168.

MacBride, R.L., & Sutin, J. (1976). Projections of the locus coeruleus and adjacent pontine tegmentum in the cat. Journal of Comparative Neurology, 165 265-284.

Maffei, L., & Fiorentini, A. (1976). Asymmetry of motility of the eyes, and change in the binocular properties of cortical cells in adult cats. Brain Research, 105, 73-78.

Malcolm, L.J., Bruce, J.S., & Burke, W. (1970). Excitability of the lateral geniculate nucleus in the alert, nonalert and sleeping cat. Experimental Brain Research, 40, 283-297.

Mancia, M., Broggi, G., & Margnelli, M. (1971). Brainstem reticular effect on intralaminar thalamic neurons in the cat. Brain Research, 25, 638-641.

Mangel, S.C., Wilson, J., and Sherman, S.M. (1983). Development of neuronal response properties in the lateral geniculate nucleus during monocular deprivation. Journal of Neurophysiology, 50, 496-502.

Moore, R., & Bloom, F. (1979). Central Catecholaminergic neuron systems: Anatomy and physiology of norepinephrine and epinephrine systems. Annual Review of Neuroscience, 2, 113-168.

Moruzzi, G. (1964). Reticular influences on the EEG. Electroencephalography and Clinical Neurophysiology, 16, 2-17.

Moruzzi, G., & Magoun, H.W. (1949). Brainstem reticular formation and activation of the EEG. Electroencephalography and Clinical Neurophysiology, 1, 455-473.

Mukhametov, L., Rizzolati, G., & Tradardi, V. (1970). Spontaneous activity of neurons of nucleus reticularis thalami in freely behaving cats. Journal of Physiology (London), 210, 651-667.

Munsen, J.B., & Graham, R.B. (1971). Lateral geniculate spikes in sleeping awake, and reserpine treated cats: Correlated excitability changes in superior colliculus and related structures. Experimental Neurology, 31, 326-336.

Munsen, J.B., & Schwartz, K.S. (1972). Lateral geniculate and occipital cortex spikes with eye movements in awake and sleeping cats. Temporal and functional correlations. Experimental Neurology, 35, 300-304.

Nakai, Y., & Domino, E.F. (1968). Reticular facilitation of visually evoked responses by optic tract stimulation before and after enucleation. Experimental Neurology, 22, 532-544.

Negeshi, K., Lu, E.S. and Verzeano, M. (1962). Neuronal activity in the lateral geniculate body and nucleus reticularis of the thalamus. Vision Research, 1, 343-353.

Nicol, R., & Wojtowicz, M. (1980). Barbiturates and GABA-ergic mechanisms. Brain Research, 191, 235-237.

Orban, G., Vandebussche, E., & Callens, M. (1972). Electrophysiological evidence for the existance of connections between the brainstem oculomotor centers and the visual system in the cat. Brain Research, 41, 225-229.

Orem, J., Schlag-Rey, M. & Schlag, J. (1973). Unilateral visual neglect and thalamic interlaminar lesions in the cat. Journal of Experimental Neurology, 40, 184-197.

Pettigrew, J.D. (1972). The importance of early visual experience for neurons in the developing geniculostriate system. Investgative Ophthalmology, 11, 368-393.

Pettigrew, J.D., & Kasamatsu, T. (1978). Local perfusion of noradrenalin maintains visual cortical plasticity. Nature, 271, 761-763.

Porter, J., & Spencer, R. (1982). Localization and morphology of cat extraocular muscle afferent neurons identified by retrograde transport of horseradish peroxidase. Journal of Comparative Neurology, 204, 56-64.

Rapisardi, S.C., Wilson, P.D., & Alvarez. (1974). Reticular modulation of evoked potentials at the cortex and lateral geniculate nucleus of the unanesthetized squirrel monkey. Experimental Neurology, 44, 282-294.

Richard, D., Gioanni, Y., Kitsikis, A., & Buser, P. (1975). A study of geniculate unit activity during cryogenic blockade of the primary visual cortex in the cat. Experimental Brain Research, 22, 235-242.

Richards, C. (1972). On the mechanism of barbiturate anesthesia. Journal of physiology, 227, 749-767.

Rodieck, R. (1979). Visual pathways. Annual Review of Neuroscience, 2, 193-225.

Rodieck, R.W., & Dreher, B. (1979). Visual suppression from the nondominant eye in the lateral geniculate nucleus: a comparison of cat and monkey. Experimental Brain Research, 35, 465-477.

Salinger, W.L., Garraghty, P.E., MacAvoy, M.G., & Hooker, L.F. (1980). Sensitivity fo the mature lateral geniculate nucleus to components of monocular paralysis. Brain Research, 187, 307-320.

Salinger, W.L., Garraghty, P.E., and Schwartz, M.A. (1980). Response of the mature lateral geniculate nucleus to monocular paralysis: Contribution of nonretinal and retinal components. Brain Research, 192, 255-260.

Salinger, W.L., Schwartz, M.A., & Wilkerson, P.R. (1977a). Selective cell loss in the lateral geniculate nucleus of adult cats after chronic monocular paralysis. Brain Research, 125, 257-263.

Salinger, W.L., Schwartz, M.A., & Wilkerson, P.R. (1977b). Selective loss of lateral geniculate nucleus cells after binocular lid suture. Brain Research, 130, 81-88.

Sanderson, K.J., Bishop, P.O., & Darian-Smith, J. (1971). The properties of binocular receptive fields of lateral geniculate neurons. Experimental Brain Research, 13, 178-207.

Sanderson, K.J., Darian-Smith, I., & Bihop, P.O. (1969). Binocular corresponding receptive fields of single units in the cat dorsal lateral geniculate nucleus. Vision Research, 9, 1297-1303.

Satinski, D. (1968). Reticular influences on lateral geniculate neuron activity. Electroencephalography and Clinical Neurophysiology, 25, 543-549.

Scheibel, M.E, & Scheibel, A.B. (1958). Structural substrates for integretive patterns in the brainstem reticular core. In H. Jasper, L. Proctor, R. Knighton, R. Noshay, & W. Costello (Eds.) Reticular Formation of the Brain, (pp. 31-58). Boston: Little-Brown.

Scheibel, M.E., & Scheibel, A.B. (1966). The organization of the nucleus reticularis thalami. Brain Research, 1, 43-62.

Scheibel, M.E., & Scheibel, A.B. (1967). Structure of nonspecific thalamic nuclei and their projection toward cortex. Brain Research, 6, 60-94.

Schiller, P., & Koerner, M. (1971). Discharge characteristics of single units in superior colliculus of alert rhesus monkeys. Journal of Physiology, 34, 920-936.

Schlag, J., & Wazak, M. (1970). Characteristics of unit responses in nucleus reticularis thalami. Brain Research, 21, 286-288.

Schmielau, F., & Singer, W. (1974). Corticofugal control of the cat lateral geniculate nucleus. Experimental Brain Research, Suppl. 23, 363.

Schmielau, F., & Singer, W. (1977). The role of visual cortex for binocular interactions in the cat lateral geniculate nucleus. Brain Research, 120, 359-361.

Schroeder, C.E., & Salinger, W.L. (1978). The X-cell loss after chronic monocular paralysis is rapidly reversed by paralysis of the second eye. Paper presented at The Association for Research in Vision and Ophthalmology Annual Meeting, Sarasota, Florida.

Schroeder, C.E., Salinger, W.L., & Garraghty, P.E. (1982). Retinogeniculate perisynaptic time and the functional significance of differences in axonal conduction velocity. Investigative Ophthalmology and Visual Science, 22, (3). 117.

Sherman, S. & Spear, P. (1982). Organization of visual pathways in normal and visually deprived cats. Physiological Reviews, 62, 738-855.

Sherman, S. & Wilson, J. (1981). Further evidence for a critical period in the development of the cat's dorsal lateral geniculate nucleus. Journal of Comparative Neurology, 196, 459-470.

Shirokawa, T. & Kasamatsu, T. (1984). Beta adrenergic receptor mediates neuronal plasticity in visual cortex. Investigative Ophthalmology and Visual Science, 25, (3), 218.

Sherman, S., Wilson, J. & Guillery, R. (1975). Evidence that binocular competition affects the postnatal development of Y-cells in the cat's lateral geniculate nucleus. Brain Research, 100, 441-444.

Singer, W. (1970). Inhibitory interaction in the lateral geniculate body of the cat. Brain Research, 18, 165-170.

Singer, W. (1973). Brainstem stimulation and the hypothesis of presynaptic inhibition in cat lateral geniculate nucleus. Brain Research, 61, 55-68.

Singer, W. (1977). Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. Physiological Reviews, 57 (3), 386-420.

Singer, W., & Bedworth, N. (1973). Inhibitory interaction between X- and Y-units in the cat lateral geniculate nucleus. Brain Research, 49, 291-307.

Singer, W., & Bedworth, N. (1974). Correlation between the effects of brainstem stimulation and saccadic eye movements on transmission in the cat lateral geniculate nucleus. Brain Research, 72, 185-202.

Singer, W. & Schmielau, F. (1976). The effect of reticular stimulation on binocular inhibition in the cat lateral geniculate body. Experimental Brain Research, 25, 221-223.

Singer, W., Tretter, F., & Cynader, M. (1976). The effect of reticular stimulation on spontaneous and evoked activity in the cat visual cortex. Brain Research 102, 71-90.

Sireteneau, R., & Fronius, M. (1981). Nasotemporal asymmetries in human amblyopia: Consequences of long term interocular suppression. Vision Research, 21, 1055-1063.

Sireteneau, R., & Singer, W. (1984). Impaired visual responsiveness in both eyes of kittens with unilateral surgically induced strabismus. Investigative Ophthalmology and Visual Science, 23, (3), 216.

Skinner, J.E, & Yingling, C.D. (1977). Central gating mechanisms that regulate event related potentials and behavior. In J. Desmedt (Ed.) Progress in Clinical Neurophysiology: Vol. 1. Attention, voluntary contraction, and event-related potentials, (pp. 30-69). Basel: Karger.

So, Y.T., & Shapley, R.M. (1979). Spatial properties of X- and Y-cells in the lateral geniculate nucleus of the cat and the conduction velocities of their inputs. Experimental Brain Research, 36, 533-550.

Steinbach, M, & Smith, D. (1981). Spatial localization after strabismus surgery: Evidence for inflow. Science, 213, 1407-1408.

Stewart, O., Cotman, C., & Lynch, G. (1973). Re-establishment of electrophysiologically functional entorhinal cortical input to dentate gyrus deafferented by ipsilateral entorhinal lesions: Innervation by contralateral entorhinal cortex. Experimental Brain Research. 18, 396-414.

Stone, J., Dreher, B., & Levinthal, A. (1979). Hierarchical and parallel mechanisms in the organization of visual cortex. Brain Research Reviews, 1, 345-394

Suzuki, H., & Takahashi, M. (1970). Organization of lateral geniculate neurons in binocular inhibition. Brain Research, 23, 261-264.

Syka, J., Popelar, J., & Radil-Weiss, T. (1975). Influence of increasing doses of pentobarbital on the midbrain reticular formation in rats: Spontaneous firing of neural pairs and activity evoked by polarization. Brain Research, 88, 263-279.

Szentagothai, J. (1973). Architecture of the lateral geniculate nucleus. In R. Jung (Ed.) Handbook of Sensory Physiology, (vol. 7, pp. 141-176). St. Louis: Mosby.

Szentagothai, J., Hamori, J., & Tombol, T. (1966). Degeneration and electron microscope analysis of the synaptic glomeruli in the lateral geniculate body. Experimental Brain Research, 2, 283-301.

Tsumoto, T., Creutzfelt, O. & Legendy, C. (1978). Functional organization of the corticofugal system from visual cortex to the LGN in the cat. Experimental Brain Research, 32, 345-364.

Tsumoto, T., & Suzuki, D.A. (1976). Effects of frontal eye field stimulation upon activities of the lateral geniculate body of the cat. Experimental Brain Research, 25, 291-306.

Updyke, B.V. (1975). The patterns of projection of cortical areas 17, 18, and 19 onto the laminae of the dorsal lateral geniculate nucleus of the cat. Journal of Comparative Neurology, 163, 377-396.

Von Norden, G. (1980). Special forms of strabismus. in B. Burian and G. Von Norden (eds.) Binocular vision and ocular motility: Theory and management of strabismus, (2nd ed., pp. 429-449). St Louis: Mosby.

Westheimer, G. (1963). Amphetamines, barbiturates and accommodation-convergence. Arch. Ophthal., 70, 830-836.

Wilkerson, P.R., Salinger, W.L., & MacAvoy, M.G. (1977). Monocular and binocular paralysis produce different patterns of change in the lateral geniculate nucleus of adult cats. Paper presented at Society for the Neurosciences Annual Meeting, Anaheim, California.

Wilson, P.D., Rowe, M.H., & Stone, J. (1976). Properties of relay cells in the cat's lateral geniculate nucleus: A comparison of W-cells with X- and Y-cells. Journal of Neurophysiology, 39, 1193-1209.

Yingling, C.D., & Skinner, J.E. (1975). Regulation of unit activity in nucleus reticularis thalami by mesencephalic reticular formation and frontal granular cortex. Electroencephalography and Clinical Neurophysiology, 39, 635-642.

APPENDIX A.

Percentages of X-cells and of Y-cells, encountered in each acute and chronic monocularly paralyzed animal, under unanesthetized (#) and anesthetized (*) experimental conditions.

Acute monocular paralysis

Subject no.	X-cells (#)	X-cells (*)	Y-cells (#)	Y-cells (*)
1	27.3%	50.0%	72.7%	50.0%
2	69.6%	57.1%	72.7%	50.0%
3	54.5%	50.0%	45.5%	50.0%
4	64.3%	63.2%	35.7%	36.8%
5	62.5%	85.5%	37.5%	14.3%

Chronic monocular paralysis

subject no.	X-cells (#)	X-cells (*)	Y-cells (#)	Y-cells (*)
1	10.3%	60.0%	89.7%	40.0%
2	21.7%	60.0%	78.3%	40.0%
3	19.2%	64.3%	80.8%	35.7%
4	20.0%	50.0%	80.0%	50.0%