

20030128 396

DTIC FILE COPY

(4)

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

AD-A204 177

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER #47	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Experience-dependent Modifications of Kitten Striate Cortex are not Prevented by Thalamic Lesions that Include the Intralaminar Nuclei		5. TYPE OF REPORT & PERIOD COVERED Technical Report
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) M.F. Bear, A. Kleinschmidt and W. Singer		8. CONTRACT OR GRANT NUMBER(s) N00014-86-K-0041
9. PERFORMING ORGANIZATION NAME AND ADDRESS Center for Neural Science Brown University Providence, Rhode Island 02912		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS N-201-484
11. CONTROLLING OFFICE NAME AND ADDRESS Personnel and Training and Rsch. Program Office of Naval Research, Code 442PT Arlington, Virginia 32217		12. REPORT DATE January 31, 1989
		13. NUMBER OF PAGES 17 pages
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report)
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited. Publication in part or in whole is permitted for any purpose of the United States Government.		
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)		
18. SUPPLEMENTARY NOTES Published in Experimental Brain Research.		
19. KEY WORDS (Continue on reverse side if necessary; use and identify by block number) Visual Cortex Development Plasticity Intralaminar Nuclei Kitten		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) It has been shown previously that surgical lesions of the antero-medial thalamus interfere with ocular dominance modifications that normally result from monocular deprivation in young kittens (Singer 1982). The aim of the present study was to determine whether this effect was due specifically to the destruction of the visual cortical projections of the anterior intralaminar nuclei. We report here that large excitotoxin lesions of the anterior dorsal thalamus have no effect on the cortical response to monocular deprivation. These data indicate that the intralaminar projection is not essential for ocular dominance plasticity.		

DTIC
ELECTED
3 FEB 1989
A

DD FORM 1 JAN 73 1473

EDITION OF 1 NOV 65 IS OBSOLETE

S/N 0102-LF-014-6601

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

89 2 3 110

Best Available Copy

**Experience-dependent modifications of kitten striate
cortex are not prevented by thalamic lesions that
include the intralaminar nuclei.**

Mark F. Bear¹, Andreas Kleinschmidt and Wolf Singer

**Max-Planck-Institut Für Hirnforschung
Deutschordenstrasse 46
6000 Frankfurt 71**

¹Mark F. Bear was supported in part by U.S. Office of Naval Research
Contract N00014-86-K-0041. Present address: Center for Neural Science,
P.O. Box 1953, Brown University, Providence, RI 02912.

Abstract

It has been shown previously that surgical lesions of the antero-medial thalamus interfere with ocular dominance modifications that normally result from monocular deprivation in young kittens (Singer, 1982). The aim of the present study was to determine whether this effect was due specifically to the destruction of the visual cortical projections of the anterior intralaminar nuclei. We report here that large excitotoxin lesions of the anterior dorsal thalamus have no effect on the cortical response to monocular deprivation. These data indicate that the intralaminar projection is not essential for ocular dominance plasticity.

Cont'd Pg. 4



A-1

Introduction

The modification of visual cortical organization by sensory experience is recognized to be an important component of early postnatal development. It is apparent, however, that these experience-dependent modifications are influenced profoundly by signals of non-retinal origin. For instance, an ocular dominance (OD) shift in area 17 after monocular deprivation (MD) seems to require that the animal attends to visual stimuli and uses vision to guide behavior (Singer, 1979; Singer et al., 1982; Singer, 1982). These observations have led to the idea that modifications of the visual cortex depend upon the presence of extra-retinal "gating" signals which convey information about the behavioral state of the animal (Singer, 1979).

Over the past several years, we have sought to identify the neural substrate of these gating signals. Naturally, our attention has been focused on the non-geniculate afferent projections to striate cortex. One such projection arises from the intralaminar nuclei of the dorsal thalamus. The idea that these thalamic nuclei provide the necessary extra-retinal signals is attractive for a number of reasons. For instance, the intralaminar nuclei project diffusely to all of the neocortex (Jones and Leavitt, 1974; Kaufman and Rosenquist, 1984a), receive direct connections from the midbrain reticular formation (MRF; Edwards and DeOlmos, 1976; Steriade and Glenn, 1982; Kaufman and Rosenquist, 1984b), and are thought to mediate reticular activation of the cortical EEG (Moruzzi, 1972; Glenn and Steriade, 1982). Moreover, electrical stimulation of the intralaminar nuclei produces conjugate saccadic eye movements (Schlag and Schlag-Rey, 1971), and a substantial enhancement of visually evoked potentials in area 17 (Singer and Rauschecker, 1982).

→ The intralaminar projection to striate cortex arises from the central lateral (CL), central medial (CM) and paracentral (PC) nuclei, which are embedded in the internal medullary lamina (IML) of the thalamus. (Cunningham and LeVay, 1987). In the present study, we have examined the possible involvement of these intralaminar nuclei in visual cortical plasticity by producing lesions of the thalamus with the excitotoxin N-methyl aspartate (NMA) ~~which~~ destroys neurons, but spares axons of passage (Nadler, et al., 1981). Our strategy was to destroy all the portions of the CL-PC complex that project to area 17, and then test for a deficit in the OD shift that normally occurs after 7-10 days of MD. (AW) ↗

Materials and Methods

Six kittens were used in this study (Table 1). Three kittens were reared in the dark prior to the thalamic lesions; three animals were reared normally in the lighted colony. At 4-5 weeks of age, each animal was anesthetized with a ketamine-xylazine mixture and placed in a stereotaxic head-holder. A small hole was drilled in the skull and a 5 μ l Hamilton syringe was lowered to a position 12 mm above the interaural line at A3 and L3. 1-2 μ l of a 50 μ g/ μ l solution of NMA (pH ~ 7) was injected rapidly over 5 minutes into the thalamus on the left side. The needle was withdrawn and the right eyelid was sutured closed.

Approximately 10 days later, each kitten was prepared for a routine ocular dominance assay of striate cortex. Details of the surgical preparation may be found elsewhere (Singer, 1982). During the recording session, the kittens were artificially respired on 70% nitrous oxide and 30% oxygen, and received a continuous intravenous infusion of Nembutal (2 mg/ kg/ hr) and Imbretil (1 mg/

kg/ hr) in Ringer's solution. The EEG, ECG and expired CO₂ were monitored continuously. Single units were recorded from area 17 with micropipettes filled with 1.5 M potassium chloride (impedance ~ 15 MΩ). Long electrode penetrations, angled obliquely, were made down the medial bank of the postlateral gyrus through the area centralis representation. Each unit encountered along this track was assigned to one of 5 ocular dominance groups. Neurons in groups 1 and 5 were activated by stimulation of the deprived or non-deprived eyes, respectively, but not both. Neurons assigned to group 3 were activated equally strongly by stimulation of either eye. Cells in groups 2 and 4 were binocular but dominated by either the deprived or non-deprived eyes, respectively. In addition, each unit was classified subjectively for response quality, orientation and velocity tuning, spontaneous activity, and receptive field type ("simple" or "complex").

In 3 out of 6 cases we also tested for reticular facilitation of cortical evoked potentials recorded through surface EEG electrodes positioned at L2 and L12 on each side (AP0). Bipolar concentric stimulating electrodes were inserted stereotaxically into the optic chiasm and in the MRF (A2, L2, V2). Stimulus pulses were delivered through these electrodes that had a duration of 50 μsec and an intensity of between 50 to 200 μA (see Singer et al., 1976 for further details).

At the end of the recording session, the animal was killed with an overdose of sodium pentobarbital and was perfused through the ascending aorta with 10% buffered formalin (pH 7.4). The brain was subsequently sectioned in the coronal plane. The sections were mounted onto microscope slides and stained for Nissl substance with cresyl violet acetate. The thalamic sections were

projected onto paper and drawn. The extent of the thalamic lesion was reconstructed from these drawings.

Results

A representative NMA lesion of the dorsal thalamus, from kitten K162, is reconstructed in figure 1. The region of total neuronal cell loss (hatched area) includes all portions of the anterior intralaminar nuclei that project directly to visual cortex (Kaufman and Rosenquist, 1984a ; Cunningham and LeVay, 1987; Bear and Singer, personal observations). In addition, several other nuclei of the thalamus were destroyed to varying degrees including AM, VA, MD, VL, VB, VM, LA, LP, and CM (see legend of figure 1 for abbreviations). A photomicrograph of another lesion, from K163, is presented in figure 2.

The lesions produced a pronounced motor asymmetry. For the first few days after surgery, the kittens turned compulsively to the left (ipsilateral to the lesion). This motor disturbance usually subsided as the week progressed. However, even after the obvious ipsiversive turning had ceased, the animals continued to orient preferentially to the left in response to novel stimuli.

Despite the extensive thalamic damage and behavioral disruption, 10 days of monocular deprivation still produced a strong ocular dominance shift in area 17 ipsilateral to the lesion (Table 1). This was the case regardless of whether the animals had been reared previously in the darkroom or in the lighted colony. A representative OD histogram, obtained from kitten K162, is presented in figure 1(a). Other receptive field properties, like orientation and velocity tuning, were also apparently unaffected by the lesions.

At the end of the recording sessions in 3 cases (K161, K163, K182; Table 1) we tested for deficits in the MRF facilitation of cortical potentials evoked by electrical stimulation of the optic chiasm. We found no clear asymmetry in the reticular activation of the two hemispheres despite the destruction of the intralaminar nuclei on one side. A brief train of MRF stimulation (4 pulses at 15 msec intervals) elicited negative cortical potentials on both sides and facilitated the evoked responses to an optic chiasm stimulation delivered 100 msec after the MRF stimulus (data not shown).

Discussion

The aim of this study was to test the hypothesis that the projections to visual cortex from the intralaminar nuclei are essential for experience-dependent cortical modifications. To that end, we prepared animals with complete lesions of those portions of the intralaminar nuclei that anatomical studies have shown to project directly to the visual cortex (Cunningham and LeVay, 1986; Bear and Singer, unpublished observations). In no case did we find that the plastic response to 7-10 days of monocular deprivation was affected by the thalamic lesions. We conclude that intact intralaminar thalamocortical projections are not required for the normal expression of ocular dominance plasticity.

The unilateral lesions of the thalamus also produced no detectable asymmetry in the visual responsiveness of individual cortical neurons. This was unexpected, since tonic discharges of intralaminar neurons are commonly believed to increase the responsiveness of cortical neurons to sensory stimuli (Singer, 1979). One possible explanation for this could be that the intralaminar

projection is inactive under the anesthetic conditions used in our physiological recordings. Perhaps recordings in chronically-implanted awake animals would have revealed a deficit in visual responsiveness in the hemispheres ipsilateral to the lesions. However, in addition, we observed no asymmetry in the MRF facilitation of the cortical response evoked by stimulation of the optic chiasm. The polysynaptic components of the evoked potential, believed to be modulated by the "non-specific" cortical projections (Singer et al., 1976; Singer, 1979), were facilitated on both sides. These results suggest that other widely projecting subcortical cell groups make an important contribution to the reticular activation of visual cortex.

The results of the present study contrast with a previous study in which the anterior dorso-medial thalamus was aspirated in dark-reared kittens (Singer, 1982). The surgical lesions were found to retard the experience-dependent development of area 17, including the acquisition of neuronal selectivity and responsiveness as well as the modification of binocular connections after prolonged periods of monocular exposure.

How might this apparent discrepancy be explained? Both the surgical (Singer, 1982) and chemical (present study) lesions were made in the hemispheres contralateral to the deprived eye, both involved the intralaminar nuclei which project directly to visual cortex, and both produced a pronounced motor asymmetry. These factors are therefore an unlikely basis for the different results. However, surgical removal of the medial thalamus did produce a severe disruption of the pattern of cortical activation normally seen after electrical stimulation of the MRF (Singer, 1982), an effect not observed in the present study. This difference is probably due to the fact that the surgical

8

lesions disrupted fibers that traverse the medial thalamus, fibers which were spared by the excitotoxin lesions. It is possible that these same fibers convey signals which promote experience-dependent modifications of visual cortex. One candidate for this hypothetical projection is the ascending cholinergic projection from the midbrain to the basal telencephalon (Woolf and Butcher, 1986).

Recently, we discovered that surgical transection of the white matter of the cingulate gyrus (the cingulum bundle) will retard the ocular dominance shift in area 17 that normally results from brief periods of monocular deprivation (Bear and Singer, 1986). These data suggest that a common final path of extra-retinal influences over visual cortical modification may be the cingulum bundle. We know that two components of this pathway are a cholinergic projection from the basal telencephalon and a noradrenergic projection from the locus coeruleus. Subcortical lesions of these two projections also interfere with OD modifications. Perhaps the surgical lesions of the thalamus affected OD plasticity by disrupting, directly or indirectly, the cholinergic and noradrenergic inputs to visual cortex. This hypothesis awaits testing.

The present study demonstrates that intralaminar projections are not *essential* for the modification of visual cortex by experience. However, this is not to say that this system does not contribute importantly to the extra-retinal modulation of cortical plasticity. We have obtained evidence very recently which indicates that ocular dominance modifications require the activation of cortical N-methyl-D-aspartate (NMDA) receptors (Kleinschmidt et al., 1987). NMDA receptors normally become effective only upon sufficient postsynaptic membrane depolarization (Dingledine, 1983). Thus, intralaminar, basal forebrain and

9

noradrenergic projections could all facilitate synaptic modifications by raising cortical excitability enough for NMDA receptors to become active. It may be that only upon the removal of two or more of these systems is cortical activity reduced sufficiently to interfere with this mechanism of synaptic modification.

References

Bear MF, Singer W (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* 320: 172-176.

Cunningham ET, LeVay S (1986) Laminar and synaptic organization of the projection from the thalamic nucleus centralis to primary visual cortex in the cat. *J. Comp. Neurol.* 254: 65-77.

Dingledine R (1983) N-methyl-aspartate activates voltage-dependent calcium conductance in rat hippocampal pyramidal cells. *J. Physiol. (Lond.)* 343: 385-405.

Edwards SB, deOlmos JS (1976) Autoradiographic studies of the projections of the midbrain reticular formation: ascending projection from the nucleus cuneiformis. *J. Comp. Neurol.* 165: 417-432.

Glenn LL, Steriade M (1982) Discharge rate and excitability of cortically projecting intralaminar thalamic neurons during waking and sleep states. *J. Neurosci.* 2: 1387-1404.

Jones EG, Leavitt RY (1974) Retrograde axonal transport and the demonstration of non-specific projections to cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey. *J. Comp. Neurol.* 154: 349-378.

Kaufman EFS, Rosenquist AC (1984a) Efferent projections of the thalamic intralaminar nuclei in the cat. *Brain Res.* 335: 257-279.

Kaufman EFS, Rosenquist AC (1984b) Afferent connections of the thalamic intralaminar nuclei in the cat. *Brain Res.* 335: 281-296.

Kleinschmidt A, Bear MF, Singer W (1987) Blockade of cortical "NMDA" receptors disrupts experience-dependent plasticity of kitten striate cortex. *Science*, in press.

Moruzzi G (1972) The sleep-waking cycle. *Ergeb. Physiol. Biol. Chem. Exp. Pharmacol.* 64: 1-165.

Nadler JV, Evenson DA, Cuthbertson G.I (1981) Comparative toxicity of kainic acid and other acidic amino acids toward rat hippocampal neurons. *Neurosci.* 6: 2505-2517.

Schlag J, Schlag-Rey (1971) Induction of oculomotor responses from thalamic internal medullary lamina in the cat. *Exp. Neurol.* 33: 408-508.

Singer W (1979) Central-core control of visual cortex functions. In: Schmidt FO, Worden FG (eds) *The Neurosciences, 4th Study Program*. MIT Press, Cambridge, pp 1093-1110.

Singer W (1982) Central-core control of developmental plasticity in the kitten visual cortex: I. Diencephalic lesions. *Exp. Brain Res.* 47: 209-222.

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

Singer W, Treter F, Yinon U (1982) Central-gating of developmental plasticity in kitten visual cortex. *J. Physiol. (Lond.)* 324: 221-237.

Steriade M, Glenn I.L (1982) Neocortical and caudate projections of intralaminar thalamic neurons and their synaptic excitation from midbrain reticular core. *J. Neurophysiol.* 48: 352-371.

Wolf NJ, Butcher LL (1985) Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thalamus, tectum, basal ganglia, and basal forebrain. *Brain Res. Bull.* 16: 603-637.

Table

Animal	Rearing	Lesion	MD	N	U	B	OED
K162L	NR	35	35-45	31	5	.19	.86
K161L	NR	31	34-41	30	7	.42	.58
K163L	NR	36	36-46	33	2	.33	.66
K180L	DR	26	26-32	30	3	.15	.78
K181L	DR	26	26-34	21	3	.33	.81
K182L	DR	26	26-39	29	1	.43	.70

Indicated for each kitten studied are the type of rearing conditions experienced before the thalamic lesion (NR: normal rearing; DR: dark-rearing), the age when the lesion was made (in days postnatal); the period of monocular deprivation (MD, in days postnatal); the total number of units studied in the striate cortex (N), the number of units which were unclassifiable with visual stimuli (U), the binocularity (B, defined as the number of cells in OD groups 2-4 divided by the total number of classifiable cells), and the open eye dominance (OED, defined as the number of cells in the monocular open eye group (group 5) plus 0.5x the number of cells in group 4 divided by the total number of classifiable neurons). The mean OED of the experimental hemispheres was 0.75 ± 0.04 (SEM) which is not significantly different from the value calculated from the control hemispheres of a previous study ($OED = 0.77 \pm 0.04$, $n = 8$, Bear and Singer, 1986).

Figure Legends

Figure 1: (A) Ocular dominance histogram from a kitten (K162, table 1) that received a thalamic lesion on postnatal day 35 and was subsequently monocularly deprived. 10 days of MD shifted the OD profile strongly to the groups dominated by the non-deprived eye (groups 4 & 5). (B) Reconstruction of the lesion that resulted from the injection of NMA into the thalamus. The regions of neuronal cell loss are indicated by hatching. The lesion included the portions of the intralaminar nuclei that project to visual cortex (Cunningham and LeVay, 1986; Bear and Singer, unpublished observations). *Abbreviations:* AV: anterior ventral nucleus; AM: anterior medial nucleus; Ca: caudate; CL: central lateral nucleus; CM: centre médian nucleus; CP: cerebral peduncle; ENT: entopeduncular nucleus; GL: lateral geniculate nucleus; GM: medial geniculate nucleus; Ha: habenula; IC: internal capsule; LA: lateral anterior nucleus; LP: lateral posterior nucleus; MD: medial dorsal nucleus; OT: optic tract; PC: paracentral nucleus; Pul: pulvinar nucleus; R: reticular nucleus; VA: ventral anterior nucleus; VB: ventrobasal complex; VL: ventral lateral nucleus; VM: ventral medial nucleus.

Figure 2: Low magnification (5x) photomicrograph of a coronal section through the thalamus of kitten K163 stained for Nissl substance. The NMA lesion appears as a dark region due to gliosis. Note that the region of neuronal cell loss includes the anterior intralaminar nuclei, CL and PC, on the left side. See figure 1 for abbreviations.

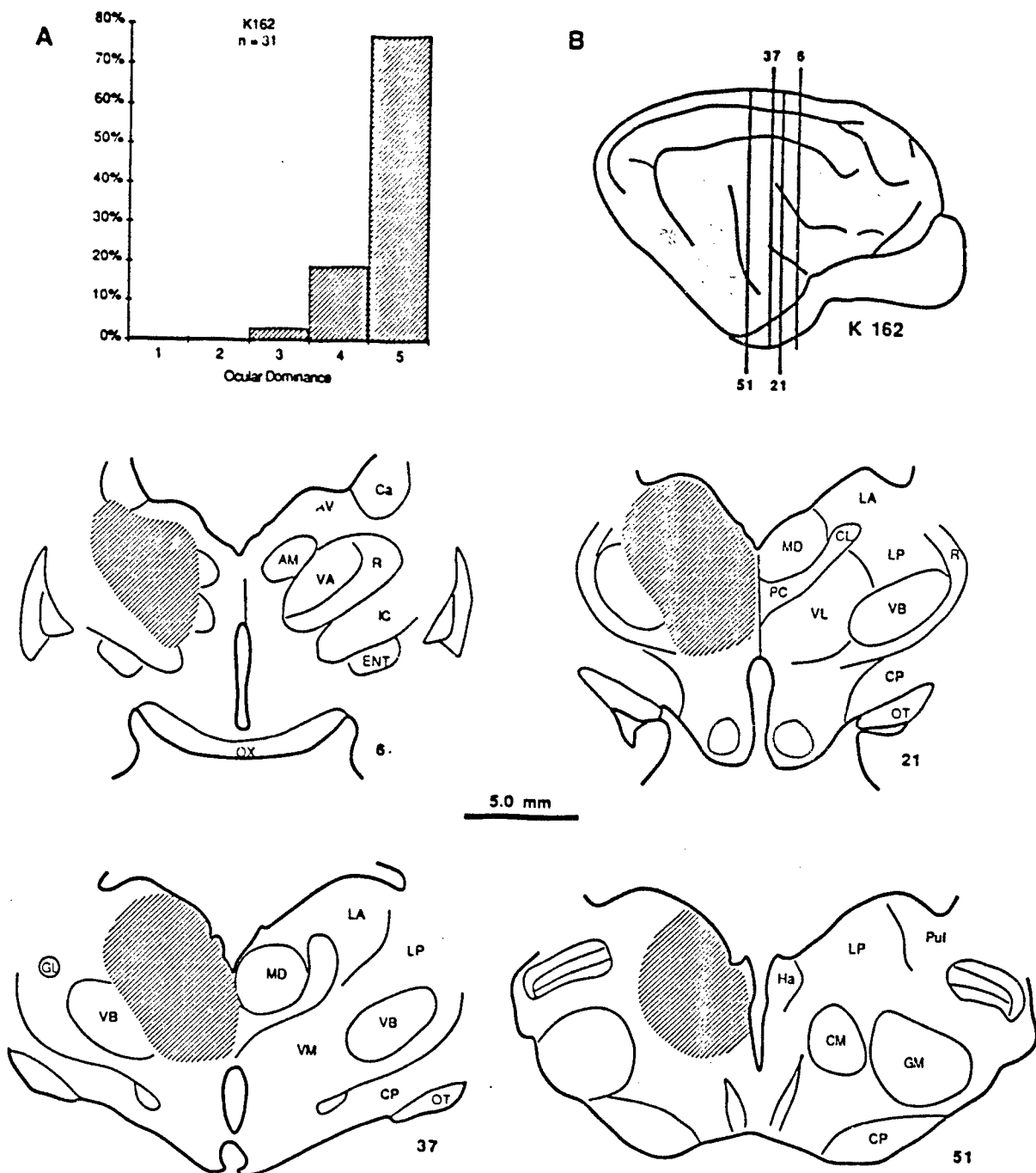


Fig. 1. A Ocular dominance histogram from a kitten (K162, Table 1) that received a thalamic lesion on postnatal day 35 and was subsequently monocularly deprived. 10 days of MD shifted the OD profile strongly to the groups dominated by the non-deprived eye (groups 4 and 5). B Reconstruction of the lesion that resulted from the injection of NMA into the thalamus. The regions of neuronal cell loss are indicated by hatching. The lesion included the portions of the intralaminar nuclei that project to visual cortex (Cunningham and LeVay, 1986; Bear and Singer, unpublished observations).

Abbreviations: AV: anterior ventral nucleus; AM: anterior medial nucleus; Ca: caudate; CL: central lateral nucleus; CM: centre médian nucleus; CP: cerebral peduncle; ENT: entopeduncular nucleus; GL: lateral geniculate nucleus; GM: medial geniculate nucleus; Ha: habenula; IC: internal capsule; LA: lateral anterior nucleus; LP: lateral posterior nucleus; MD: medial dorsal nucleus; OT: optic tract; PC: paracentral nucleus; Pul: pulvinar nucleus; R: reticular nucleus; VA: ventral anterior nucleus; VB: ventrobasal complex; VL: ventral lateral nucleus; VM: ventral medial nucleus; OX: optic chiasm

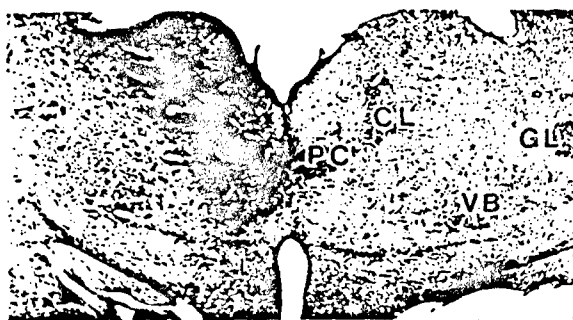


Fig. 2. Low magnification (5 ×) photomicrograph of a coronal section through the thalamus of kitten K163 stained for Nissl substance. The NMA lesion appears as a dark region due to gliosis. Note that the region of neuronal cell loss includes the anterior intralaminar nuclei, CL and PC, on the left side. See Fig. 1 for abbreviations